



CHEST[®] Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



Courtesy Dr. Jonathan Corren

It took longer for those treated with tezepelumab to have a first exacerbation, noted Dr. Corren and colleagues.

Tezepelumab reduces exacerbations in asthma

BY BIANCA NOGRADY

Frontline Medical News

Patients whose asthma remains uncontrolled despite treatment may benefit from a new monoclonal antibody that targets an inflammatory cytokine known to be promoted in asthmatic airways, according to data presented at the annual congress of the European Respiratory Society.

Writing in the Sept. 7 issue of the *New England Journal of Medicine*, researchers reported on a phase 2, randomized placebo-controlled trial of three dosing regimens of subcutaneous tezepelumab, which targets the epithelial cell-derived cytokine thymic stro-

mal lymphopoietin (TSLP). The trial involved 584 patients with uncontrolled asthma, despite treatment with long-acting beta-agonists and medium to high doses of inhaled glucocorticoids.

The investigators found that exacerbation rates were significantly lower for all three doses of tezepelumab, compared with placebo, with an overall 34% reduction in the risk of exacerbation with tezepelumab (*N Engl J Med*. 2017;377:936-46).

At 70 mg every 4 weeks, exacerbation rates were 61% lower than in the placebo group; at 210 mg every 4 weeks, they were 71% lower; and at 280 mg every 2 weeks, they were 66% lower

TIME TO FIRST EXACERBATION UPPED // continued on page 4

Statins linked to lower death rates in COPD

BY AMY KARON

Frontline Medical News

FROM CHEST ■ Receiving a statin prescription within a year after diagnosis of chronic obstructive pulmonary disease was associated with a 21% decrease in the subsequent risk of all-cause mortality and a 45% drop in risk of pulmonary mortality, according to the results of a large retrospective administrative database study.

The findings belie those of the recent Simvastatin in the Prevention of COPD Exacerbation (STATCOPE) trial, in which daily simvastatin (40 mg) did not affect exacerbation rates or time to first exacerbation in high-risk COPD patients, wrote Larry D. Lynd, PhD, a professor at the University of British Columbia, Vancouver, and his associates. Their study was observational, but the association between statin use and decreased mortality “persisted across several measures of statin exposure,” they wrote. “Our findings, in conjunction with previously reported evidence, suggest that there may be a specific subtype of COPD patients that may benefit from statin use.” The study appears in the September issue of *CHEST* (2017;152:486-93).

COPD affects about 12% of adults aged 30

MOST RECEIVED ATORVASTATIN // continued on page 6

INSIDE HIGHLIGHT



NEWS FROM CHEST

An interview with the incoming CHEST President

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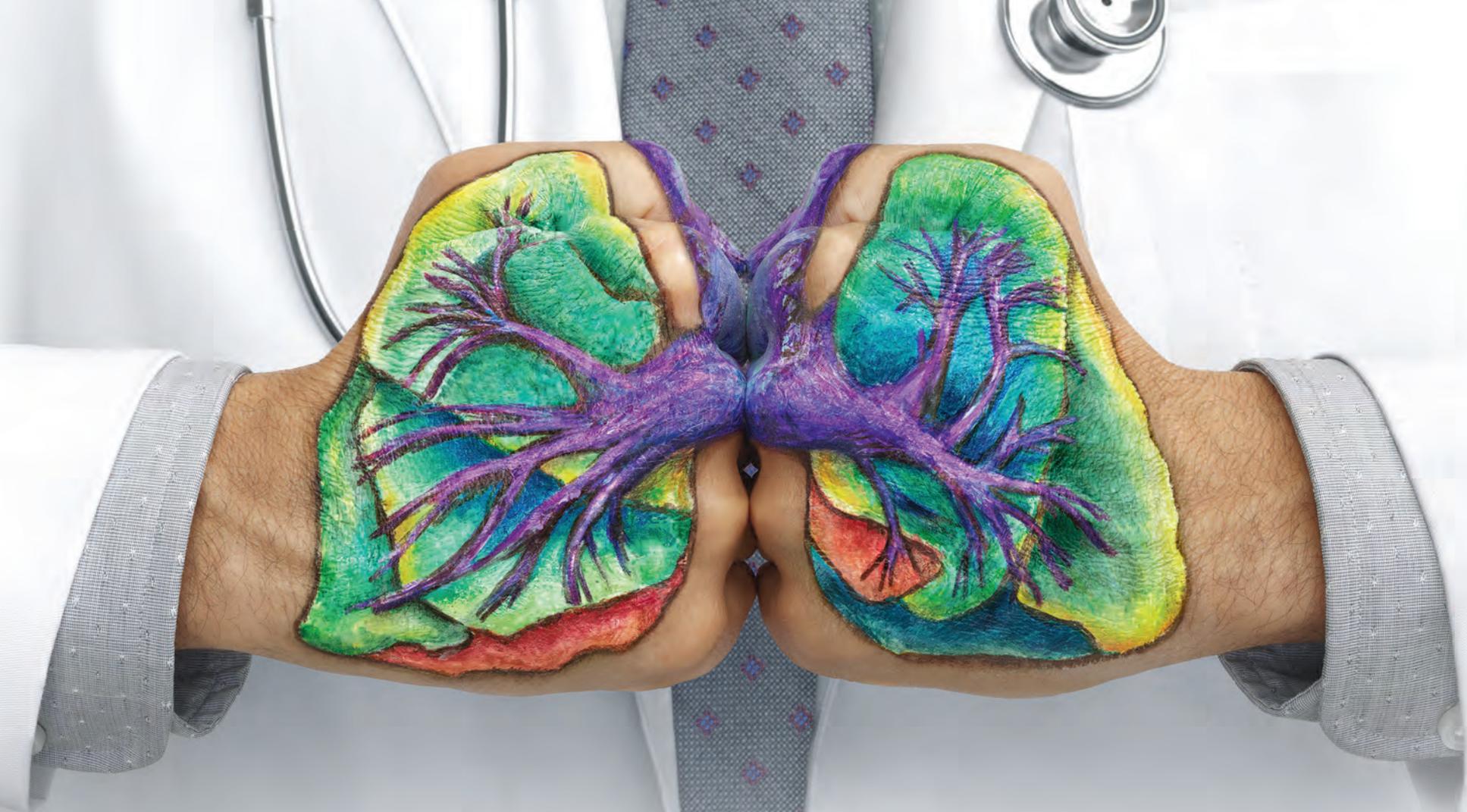
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Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST $>3\times$ ULN have been reported in patients treated with Esbriet. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or AST than placebo patients (3.7% vs 0.8%, respectively). No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the

placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions ($\geq 10\%$) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and

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WE WON'T BACK DOWN FROM IPF

Help preserve more lung function. Reduce lung function decline.¹⁻⁴

STUDIED IN A RANGE OF PATIENTS



Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications¹

DEMONSTRATED EFFICACY



In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF^{1-4*}

ESTABLISHED SAFETY AND TOLERABILITY



The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials^{2†}

COMMITTED TO PATIENTS



Genentech offers a breadth of patient support and assistance services to help your patients with IPF[‡]

WORLDWIDE PATIENT EXPERIENCE



More than 31,000 patients have taken pirfenidone worldwide[§]

pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal diseases requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

References: 1. Data on file. Genentech, Inc. 2016. 2. Esbriet Prescribing Information. Genentech, Inc. January 2017. 3. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med*. 2014;371(12):1172]. *N Engl J Med*. 2014;370(22):2083–2092. 4. Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760–1769.

Learn more about Esbriet and how to access medication at EsbrietHCP.com

IPF=idiopathic pulmonary fibrosis.

*The safety and efficacy of Esbriet were evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in which 1247 patients were randomized to receive Esbriet (n=623) or placebo (n=624).² In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide (%DL_{co}) between 30%–90%. The primary endpoint was change in %FVC from baseline at 52 weeks.³ In CAPACITY 004, 348 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and %DL_{co} ≥35%. For both CAPACITY trials, the primary endpoint was change in %FVC from baseline at 72 weeks.⁴ Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.^{2,3} Esbriet demonstrated a significant effect on lung function for up to 72 weeks in CAPACITY 004, as measured by %FVC and mean change in FVC (mL).^{1,2,4} **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006.**^{2,4}

[†]In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).²

[‡]Esbriet Access Solutions offers a range of access and reimbursement support for your patients and practice. Clinical Coordinators are available to educate patients with IPF. The Esbriet[®] Inspiration Program[™] motivates patients to stay on treatment.

[§]The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.²

Esbriet[®]
(pirfenidone) tablets 267 mg
801 mg

“The observed improvements in disease control in patients who received tezepelumab highlight the potential pathogenic role of TSLP across different asthma phenotypes,” said Dr. Jonathan Corren.

Time to first exacerbation upped // *continued from page 1*

(*P* was less than .001 in comparisons between each group and the placebo).

The overall annualized exacerbation rates by week 52 were 0.26 for the 70-mg group, 0.19 for the 210-mg group, and 0.22 for the 280-mg group, compared with 0.67

in the placebo group, regardless of a patient’s baseline eosinophil count. Patients treated with tezepelumab had a longer time to first asthma exacerbation. They also experienced a significantly higher change from baseline in their pre-bronchodilator forced expiratory

volume in 1 second at week 52, when compared with patients on the placebo.

“The observed improvements in disease control in patients who received tezepelumab highlight the potential pathogenic role of TSLP across different asthma phenotypes,”



Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

1 INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

Increases in ALT and AST $>3 \times$ ULN have been reported in patients treated with ESBRIET. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST $\geq 3 \times$ ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations $\geq 10 \times$ ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST $\geq 3 \times$ ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations [see *Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information*].

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash [see *Dosage and Administration section 2.3 in full Prescribing Information*].

5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions [see *Dosage and Administration section 2.3 in full Prescribing Information*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations [see *Warnings and Precautions (5.1)*]
- Photosensitivity Reaction or Rash [see *Warnings and Precautions (5.2)*]
- Gastrointestinal Disorders [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials

ESBRIET® (pirfenidone)

(Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common ($>1\%$) adverse reactions leading to discontinuation were rash and nausea. The most common ($>3\%$) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Table 2. Adverse Reactions Occurring in $\geq 10\%$ of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain ¹	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

¹ Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥ 5 to $<10\%$ of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during

reported Jonathan Corren, MD, of the University of California, Los Angeles, and his coauthors. "... Although TSLP is central to the regulation of type 2 immunity, many cell types that are activated by or respond to TSLP, such as mast cells, basophils, natural killer T cells, innate lymphoid cells, and neutrophils, may play a role in inflammation in asthma beyond

type 2 inflammation."

The incidences of adverse events and serious adverse events were similar across all groups in the study. Three serious adverse events – pneumonia and stroke in the same patient and one case of Guillain-Barré syndrome – in patients taking tezepelumab, were deemed to be related to the treatment.

Tezepelumab 'most promising' asthma biologic to date

Tezepelumab is the first biologic that has a substantial positive effect on two important markers of the inflammation of asthma – namely, blood eosinophil counts and the fraction of exhaled nitric oxide, noted Elisabeth H. Bel, MD, PhD, in an editorial accompanying the

New England Journal of Medicine's publication of this study (2017;377:989-91). It appears to be the broadest and most promising biologic for the treatment of persistent uncontrolled asthma to date, said Dr. Bel, of the department of respiratory medicine, Academic Medical Center, the University of Amsterdam.

The observation that tezepelumab reduces the level of both inflammatory markers shows that it hits a more upstream target and that it blocks at least two relevant inflammatory

Tezepelumab is the first biologic that has a substantial positive effect on two important markers of the inflammation of asthma, noted Elisabeth H. Bel, MD, PhD.

pathways in asthma, she noted. This is likely to be clinically relevant, since simultaneously increased exhaled nitric oxide levels and blood eosinophil counts are related to increased morbidity due to asthma.

The study was supported by tezepelumab manufacturers MedImmune (a member of the Astra-Zeneca group) and Amgen. Six of the seven authors are employees of MedImmune or Amgen. One author declared support and honoraria from several pharmaceutical companies, one declared a related patent, and five also had stock options in either MedImmune or Amgen.

Dr. Bel declared consultancies and grants from pharmaceutical companies including AstraZeneca.

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP,

comments: The impact of chronic respiratory disease on patients can be burdensome. Therapies seek to reduce this disease's impact on patients' lives.



The disease burden takes a particularly heavy toll when the response to therapies is less than optimal. Quality of life and health pay the price. The authors of this phase 2 trial advance another possible therapy which may hold promise for patients severely affected by persistent, treatment-resistant asthma.

ESBRIET® (pirfenidone)

ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see Dosage and Administration section 2.4 in full Prescribing Information].

Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information]. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended [see Dosage and Administration section 2.4 in full Prescribing Information]. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer [see Clinical Pharmacology section 12.3 in full Prescribing Information].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

Data

Animal Data

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.

ESBRIET® (pirfenidone)

8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration section 2.3 in full Prescribing Information].

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see Clinical Pharmacology section 12.3 in full Prescribing Information].

8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment [see Clinical Pharmacology section 12.3 in full Prescribing Information]. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration section 2.3 in full Prescribing Information]. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information], which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

10 OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see Warnings and Precautions (5.1)].

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required [see Warnings and Precautions (5.2)].

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required [see Warnings and Precautions (5.3)].

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information].

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Distributed by:

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years and older worldwide and is associated with increased risk of progressive cardiovascular disease and cardiovascular mortality. “Localized chronic inflammation of the airways has long been observed in COPD patients, but there is a growing understanding of systemic inflammation in a subset of patients,” the researchers noted.

For example, studies have linked chronic low-level systemic inflammation or elevated C-reactive protein levels with increased risks of severe airway obstruction, other pulmonary outcomes, and adverse cardiovascular events. Such findings prompted experts to suggest that COPD progression results from systemic inflammation, not a “spill over” of pulmonary inflammation, and that statins might help slow or block this process. Although STATCOPE did not support this idea, several prior observational studies did. Inflammation-inhibiting therapy also reduced cardiovascular events and lung cancer in the recent CANTOS trial, which this issue covers on page 7.

To further explore the question, the researchers analyzed linked health databases from nearly 40,000 patients aged 50 years and older who had received at least three prescriptions for an anticholinergic or a short-acting beta agonist in 12 months some time between 1998 and 2007. The first prescription was considered the date of COPD “diagnosis.” The average age of the patients was 71 years; 55% were female.

A total of 7,775 patients (19.6%) who met this definition of incident

“Localized chronic inflammation of the airways has long been observed in COPD patients, but there is a growing understanding of systemic inflammation in a subset of patients.”

COPD were prescribed a statin at least once during the subsequent year. These patients had a significantly reduced risk of subsequent all-cause mortality in univariate and multivariate analyses, with hazard ratios of 0.79 (95% confidence intervals, 0.68-0.91; P less than .002). Statins also showed a protective effect against pulmonary mortality, with univariate and multivariate hazard ratios of 0.52 ($P = .01$) and 0.55 ($P = .03$), respectively.

The protective effect of statins held up when the investigators narrowed the exposure period to 6 months after COPD diagnosis and when they expanded it to 18 months. Exposure to statins for 80% of the 1-year window after COPD diagnosis – a proxy for statin adherence – also led to a reduced risk of all-cause mortality, but the 95% confidence interval for the hazard ratio did not reach statistical significance (0.71-1.01; $P = .06$).

The most common prescription was for atorvastatin (49%), usually for 90 days (23%), 100 days (20%), or 30 days (15%), the researchers said. While the “possibility of the ‘healthy user’ or the ‘healthy adherer’ cannot be ignored,” they adjusted for other prescriptions, comorbidities, and income level, which should have helped eliminate this effect, they added. However, they lacked data on smoking and lung function assessments, both of which are “important confounders and contributors to mortality,” they acknowledged.

Despite [its] limitations, the study results are intriguing and in line with findings from other retrospective cohorts, noted Or Kalchier-Dekel, MD, and Robert M. Reed, MD, in an editorial published in CHEST (2017;152:456-7. doi: 10.1016/j.chest.2017.04.156).

How then can we reconcile the apparent benefits observed in retrospective studies with the lack of clinical effect seen in prospective trials, particularly the in the



DR. LYND

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP,

comments: The interplay of multiple chronic diseases contributing to a patient’s medical history is a complex one. As the provider seeks to treat the whole patient, improvements in common endpoints may occur. The observations of the authors of this study are interesting. Further study could help better understand the effects of statins in COPD patients.

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Vera A. De Palo, MD, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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CANTOS sings of new strategy for reducing CV events

BY BRUCE JANCIN

Frontline Medical News

BARCELONA – Inhibiting the interleukin-1 beta innate immunity pathway with canakinumab reduced recurrent cardiovascular events and lung cancer in the groundbreaking phase 3 CANTOS trial, Paul M. Ridker, MD, reported at the annual congress of the European Society of Cardiology.

“These data provide the first proof that inflammation inhibition in the absence of lipid lowering can improve atherogenic outcomes and potentially alter progression of some fatal cancers,” declared Dr. Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women’s Hospital, Boston, and professor of medicine at Harvard Medical School.

“Just like we’ve learned that lower LDL is better, I think we’re now learning that lower inflammation is better,” he said.

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) was a randomized, double-blind, placebo-controlled trial involving 10,061 patients in 39 countries, all of whom had a previ-

ous MI and a chronically high level of systemic inflammation as reflected in a median baseline high-sensitivity C-reactive protein (CRP) level of 4.1 mg/L. Ninety-one percent of participants were on statin therapy,

with a median LDL cholesterol of 82 mg/dL when randomized to subcutaneous canakinumab at 50, 150, or 300 mg or to placebo once every 3 months.

Canakinumab is a fully human

monoclonal antibody targeting IL-1B, a key player in systemic inflammation. The cytokine is activated by the nucleotide-binding oligomerization domain-like receptor protein 3

Continued on following page

Continued from previous page

STATCOPE study? Could it be that both negative and positive studies are “correct”? Prospective studies have thus far not been adequately powered for mortality as an endpoint, said the editorialists, who are both at the pulmonary and critical care medicine division, University of Maryland, Baltimore.

This most recent study reinforces the idea that statins may play a beneficial role in COPD, but it isn’t clear which patients to target for therapy. It is unlikely that the findings will reverse recent recommendations by the American College of Chest Physicians and Canadian Thoracic Society against the use of statins for the purpose of prevention of COPD exacerbations, but the suggestion of survival advantage related to statins certainly may breathe new life into an enthusiasm greatly tempered by STATCOPE, they said.

Canadian Institutes of Health Research supported the study. One coinvestigator disclosed consulting relationships with Teva, Pfizer, and Novartis; the others had no conflicts of interest. Neither editorialist had conflicts of interest.



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Increase in sepsis incidence stable from 2009 to 2014

BY RICHARD FRANKI

Frontline Medical News

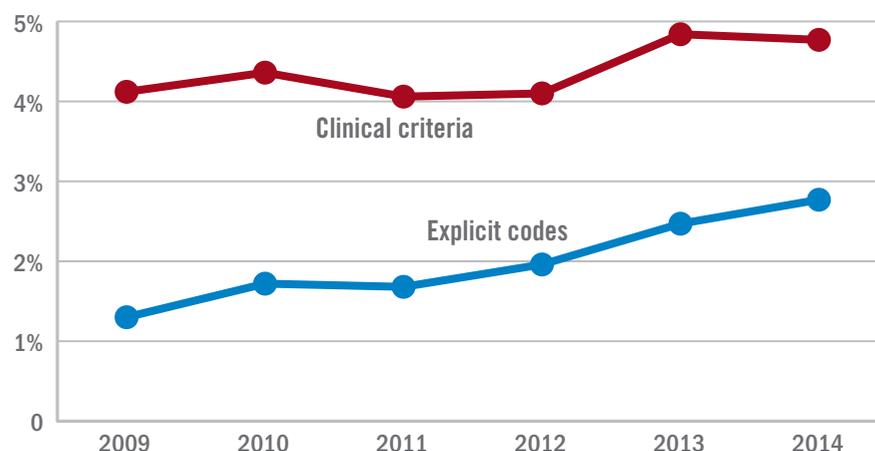
The trend for sepsis incidence from 2009 to 2014, “calculated relative to the observed 2014 rates,” was a stable increase of 0.6% per year using the more accurate of two forms of analysis, investigators reported.

The incidence of sepsis was an adjusted 5.9% among hospitalized adults in 2014, with in-hospital mortality of 15%, according to a retrospective cohort study published online Sept. 13 in JAMA.

“Most studies [of sepsis incidence] have used claims data, but increasing clinical awareness, changes in diagnosis and coding practices, and variable definitions have led to uncertainty about the accuracy of reported trends,” wrote Chanu Rhee, MD, of Harvard Medical School, Boston, and his associates (JAMA. 2017 Sep 13. doi: 10.1001/jama.2017.13836).

They used claims-based estimates using ICD-9-CM codes and clinical data from electronic health records (EHRs) to analyze data for more than 2.9 million adults

Unadjusted sepsis incidence, 2009-2014



Notes: Based on data for adults admitted to 409 academic, community, and federal hospitals. Rates for 2009-2013 calculated relative to observed 2014 rates.

Source: JAMA 2017 Sep 13. doi: 10.1001/jama.2017.13836

admitted to 409 U.S. academic, community, and federal acute-care hospitals in 2014. The claims-based explicit-codes approach used discharge diagnoses of severe sepsis (995.92) or septic shock (785.52), while the EHR-based, clinical-criteria method included blood cultures, antibiotics, and concurrent organ dysfunction with or without the criterion of a lactate

level of 2.0 mmol/L or greater.

The explicit-codes approach produced an increase of 10.3% per year in sepsis incidence from 2009 to 2014, compared with 0.6% per year for the clinical-criteria approach, while in-hospital mortality declined by 7% a year using explicit codes and 3.3% using clinical criteria, Dr. Rhee and his associates reported.

“EHR-based criteria were more

sensitive than explicit sepsis codes on medical record review, with comparable [positive predictive value]; EHR-based criteria had similar sensitivity to implicit or explicit codes combined but higher [positive predictive value],” they said. The estimates provided by Dr. Rhee and his associates lead to “a clearer understanding of trends in the incidence and mortality of sepsis in the United States but also a better understanding of the challenges in improving ICD coding to accurately document the global burden of sepsis,” Kristina E. Rudd, MD, of the University of Washington, Seattle, and her associates said in an editorial (JAMA. 2017 Sep 13. doi: 10.1001/jama.2017.13697).

The Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, National Institutes of Health, Department of Veterans Affairs, National Institutes of Health Clinical Center, and National Institute of Allergy and Infectious Diseases funded the study. Three authors received personal fees from private companies or served on advisory boards or as consultants.

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Continued from previous page

(NLRP3) inflammasome, a part of the innate immune system. Canakinumab is approved as Ilaris for treatment of several uncommon rheumatologic diseases, including cryopyrin-associated periodic syndrome and systemic juvenile idiopathic arthritis.

At a median follow-up of 3.7 years, the incidence of the primary composite efficacy endpoint of nonfatal MI, nonfatal stroke, or cardiovascular death was 4.5 events per 100 person-years in the control group, significantly higher than the 3.86 and 3.9 events per 100 person-years in patients on canakinumab at 150 and 300 mg, respectively.

Since event rates were virtually identical in the 150- and 300-mg study arms, Dr. Ridker combined those two patient groups in his analysis. They showed a 15% reduction in the risk of the primary efficacy endpoint, compared with placebo-treated controls, along with a 39% reduction from baseline in CRP. They also were 30% less likely to undergo percutaneous coronary intervention or coronary artery bypass graft during follow-up.

“That’s quite important, because

that’s a progression-of-atherosclerosis endpoint and also obviously a cost and financial endpoint,” he observed.

A key finding in CANTOS was that patients with a reduction in CRP at or exceeding the median decrease just 3 months into the study – that is, after a single injection – had a 27% reduction in major vascular events during follow-up. Patients with a lesser reduction in CRP at that point did not experience a significant reduction in the primary endpoint, compared with placebo.

“The clinician in me would say we probably ought to give a single dose of the drug, see what happens, and if you get a large inflammation reduction we could perhaps consider treating that patient, but if you did not get a large reduction perhaps this is not a therapy for that patient. Why not avoid the toxicity in people who aren’t going to respond?” Dr. Ridker said.

Side effects related to canakinumab consisted of mild leukopenia and a small but statistically significant increase in fatal infections, which he called “not surprising.”

“It’s in the same range as one gets in treating rheumatoid arthritis with a biologic drug, which rheumatologists are very comfortable doing.



Dr. Paul M. Ridker

You would imagine that, if this does become a treatment, physicians will get much better at bringing patients in early when they have signs and symptoms of infection,” the cardiologist continued.

Patients on canakinumab showed significant reductions in incident rheumatoid arthritis, gout, and osteoarthritis. The drug had no kidney or liver adverse events.

Cancer was a prespecified secondary outcome in CANTOS. The investigators saw the trial as an opportunity to test a longstanding hypothesis that inhibiting IL-1B would have a positive impact on lung cancer in particular.

“Smoking, exposure to diesel fuel,

inhalation of asbestos or other silicates – these cause inflammation which activates the NLRP3 inflammasome, but in the pulmonary system rather than the arteries,” explained Dr. Ridker, who reported serving as a consultant to Novartis.

An entry requirement in CANTOS was that patients needed to be free of known cancer. During study follow-up, 129 patients were diagnosed with lung cancer. The risk was reduced in dose-dependent fashion with canakinumab: by 39% relative to placebo in the 150-mg group and by 67% in the 300-mg group. Lung cancer mortality was reduced by 77% in the canakinumab 300-mg group.

“I don’t think this is about oncogenesis per se. I think the tumors are already there, but they don’t progress because we’ve altered the tumor’s inflammatory microenvironment,” he continued.

Simultaneous with Dr. Ridker’s presentation in Barcelona, both the atherosclerotic disease findings (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMoa1707914) and the cancer findings (Lancet. 2017 Aug 27. doi: 10.1016/S0140-6736(17)32247-X) were published.

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Bedside imaging finds best PEEP settings

BY MICHELE G. SULLIVAN

Frontline Medical News

A noninvasive bedside imaging technique can individually calibrate positive end-expiratory pressure settings in patients on extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS), a study showed.

The step-down PEEP (positive end-expiratory pressure) trial could not identify a single PEEP setting that optimally balanced lung overdistension and lung collapse for all 15 patients. But, electrical impedance tomography (EIT) allowed investigators to individually titrate PEEP settings for each patient, Guillaume Franchineau, MD, wrote (*Am J Respir Crit Care Med.* 2017;196[4]:447-57. doi: 10.1164/rccm.201605-1055OC).

“We found that EIT could provide individual, noninvasive, real-time, radiation-free lung imaging with reliable global and regional dynamic analyses of the lungs on ECMO,” wrote Dr. Franchineau of the Pierre and

Marie Curie University, Paris. “Using EIT allowed monitoring of the PEEP effect that prevented excessive lung collapse or overdistension. ... The large variability of EIT-based best compromise PEEP settings ... reinforces the notion of an individually tailored approach to mechanical ventilation. Because of the wide diversity of respiratory-system mechanical properties among patients, bedside tools for monitoring mechanical ventilation on ECMO are crucial to achieve this goal.”

The 4-month study involved 15 patients (aged, 18-79 years) who were in acute respiratory distress syndrome for a variety of reasons, including influenza (7 patients), pneumonia (3), leukemia (2), and 1 case each of *Pneumocystis*, anti-synthetase syndrome, and trauma. All patients were receiving ECMO with a constant driving pressure of 14 cm H₂O. After verifying that the inspiratory flow was 0 at the end of inspiration, PEEP was increased to 20 cm H₂O (PEEP 20) with a peak inspiratory pressure of 34 cm H₂O. PEEP₂₀ was held for 20 minutes and

then lowered by 5-cm H₂O decrements with the potential of reaching PEEP₀.

The EIT device, consisting of a silicone belt with 16 surface electrodes, was placed around the thorax aligning with the sixth intercostal parasternal space and connected to a monitor. By measuring conductivity and impedance in the underlying tissues, the device generates a low-resolution, two-dimensional image. The image was sufficient to show lung distension and collapse as the PEEP settings changed. Investigators looked for the best compromise between overdistension and collapsed zones, which they defined as the lowest pressure able to limit EIT-assessed collapse to no more than 15% with the least overdistension.

There was no one-size-fits-all PEEP setting, the authors found. The setting that minimized both overdistension and collapse was PEEP₁₅ in seven patients, PEEP₁₀ in six patients, and PEEP₅ in two patients.

At each patient's optimal PEEP setting, the median tidal volume was similar: 3.8 mL/kg ideal body weight for PEEP₁₅, 3.9 mL/kg ideal body weight for PEEP₁₀, and 4.3 mL/kg ideal body weight for PEEP₅.

Respiratory system compliance was also similar among the groups, at 20 mL/cm H₂O, 18 mL/cm H₂O, and 21 mL/cm H₂O, respectively. However, arterial partial pressure of oxygen decreased as the PEEP setting decreased, dropping from 148 mm Hg to 128 mm Hg to 100 mm Hg, respectively. Conversely, arterial partial pressure of CO₂ increased (32-41 mm Hg).

EIT also allowed clinicians to pinpoint areas of distension or collapse. As PEEP decreased, there was steady ventilation loss in the medial-dorsal and dorsal regions, which shifted to the medial-ventral and ventral regions.

“Most end-expiratory lung impedances were located in medial-dorsal and medial-ventral regions, whereas the dorsal region constantly contributed less than 10% of total end-expiratory lung impedance,” the authors noted.

“The broad variability of EIT-based best compromise PEEPs in these patients with severe ARDS reinforces the need to provide ventilation settings individually tailored to the regional ARDS-lesion distri-

bution,” they concluded. “To achieve that goal, EIT seems to be an interesting bedside noninvasive tool to provide real-time monitoring of the PEEP effect and ventilation distribution on ECMO.”

Positive PEEP trial, but questions remain

This first study to examine EIT in patients under extracorporeal membrane oxygenation shows important clinical potential, but also raises important questions, Claude Guerin, MD, wrote in an accompanying editorial. (*Am J Respir Crit Care Med.* doi: 10.1164/rccm.201701-0167ed).

The ability to titrate PEEP settings to a patient's individual needs could substantially reduce the risk of lung derecruitment or damage by overdistension.

The current study, however, has limitations that must be addressed in the next phase of research, before this technique can be adopted into clinical practice, noted Dr. Guerin, a pulmonologist at the Hospital de la Croix Rousse, Lyon, France. The 5-cm H₂O PEEP steps may be too large to detect relevant changes, he said.

In several other studies, PEEP was reduced more gradually in 2- to 3-cm H₂O increments. “Surprisingly, PEEP was reduced to 0 cm H₂O in this study, with this step main-

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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: We have learned that

patients with ARDS should be treated with mechanical ventilation in a fashion that minimizes driving pressure and optimizes

PEEP. The use of electrical impedance tomography to noninvasively inform clinicians about optimal PEEP in ARDS patients receiving extracorporeal membrane oxygenation is therefore intriguing. Conclusions are limited by the small size of this study. Further work will be needed to learn if these measurements will be generally applicable.



Doubts about pediatric CAP diagnostic practices

BY THOMAS R. COLLINS

Frontline Medical News

New studies raise doubts on the reliability of physical exam findings in suspected pediatric community-acquired pneumonia cases and on the value of blood cultures in hospitalized pediatric CAP cases.

Continued from previous page

tained for 20 minutes, raising the risk of derecruitment and further stretching once higher PEEP levels were resumed.”

The investigators did not perform any recruitment maneuvers before proceeding with PEEP adjustment. This is contrary to what has been done in prior animal and human studies.

The computation of driving pressure was done without taking total PEEP into account. “As total PEEP is frequently greater than PEEP in patients with [acute respiratory distress syndrome], driving pressure can be overestimated with the common computation.”

The optimal PEEP that the investigators aimed for was determined retrospectively from an offline analysis of the data; this technique would not be suitable for bedside management. “When ‘optimal’ PEEP was defined from [EIT criteria], from a higher Pa_O₂ [arterial partial pressure of oxygen] or from a higher compliance of the respiratory system during the decremental PEEP trial, these three criteria were observed together in only four patients with [acute respiratory distress syndrome].”

The study was done only once and cannot comply with the need for regular PEEP-level assessments over time, as could be done with some other strategies.

“Further studies should also consider taking into account the role of chest wall mechanics,” Dr. Guerin said.

Nevertheless, he concluded, EIT-based PEEP titration for each individual patient represents a prospective tool for assisting with the treatment of acute respiratory distress syndrome, and should be fully investigated in a large, prospective trial.

Dr. Franchineau reported receiving speakers fees from Mapquet. Dr. Guerin had no relevant financial disclosures.

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In one study, 128 cases of suspected CAP in children aged 3 months to 18 years presenting to an ED from July 2013 to May 2016 underwent paired assessments within 20

minutes of each other. Only 3 of 19 exam findings used to diagnose CAP – wheezing, retractions, and respiratory rate – had acceptable levels of inter-rater reliability, with

the lower end of the 95% confidential interval at a Fleiss’ kappa value of 0.4 or higher.

Eight exam findings – capillary

Continued on following page

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The safety and efficacy of UTIBRON NEOHALER in patients with asthma have not been established. UTIBRON NEOHALER is not indicated for the treatment of asthma.

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LABA = long-acting beta₂-agonist; LAMA = long-acting muscarinic antagonist.

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Continued from previous page

refill time, cough, rhonchi, head bobbing, behavior, grunting, general appearance, and decreased breath sounds – had poor to fair reliability, with a kappa of 0-0.4, the investigators found. These results came from an ongoing prospective cohort study of children with suspected CAP called Catalyzing Ambulatory Re-

search in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine, or CARPE DIEM.

“The reliability of these findings must be considered in the clinical management and research of children with CAP,” said lead author Todd Florin, MD, associate research director in emergency medicine at Cincinnati Children’s Hospital Med-

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WARNING: ASTHMA-RELATED DEATH
Long-acting beta₂-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large, placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including indacaterol, one of the active ingredients in UTIBRON NEOHALER. The safety and efficacy of UTIBRON NEOHALER in patients with asthma have not been established. UTIBRON NEOHALER is not indicated for the treatment of asthma.

Data from a large, placebo-controlled U.S. study in asthma patients showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs. A 28-week, placebo-controlled U.S. study comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol versus 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the LABAs, including indacaterol, one of the ingredients in UTIBRON NEOHALER. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with UTIBRON NEOHALER has been conducted. The safety and efficacy of UTIBRON NEOHALER in patients with asthma have not been established. UTIBRON NEOHALER is not indicated for the treatment of asthma. **Deterioration of Disease and Acute Episodes:** UTIBRON NEOHALER should not be initiated in patients with acutely deteriorating or potentially life-threatening episodes of COPD. UTIBRON NEOHALER has not been studied in patients with acutely deteriorating COPD. The initiation of UTIBRON NEOHALER in this setting is not appropriate. UTIBRON NEOHALER should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. UTIBRON NEOHALER has not been studied in the relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist. When beginning UTIBRON NEOHALER, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing UTIBRON NEOHALER, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If UTIBRON NEOHALER no longer controls the symptoms of bronchoconstriction; the patient’s inhaled, short-acting beta₂-agonist becomes less effective; or the patient needs more inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of UTIBRON NEOHALER beyond the recommended dose is not appropriate in this situation. **Excessive Use of UTIBRON NEOHALER and Use with Other Long-Acting Beta₂-Adrenergic Agonists:** As with other inhaled drugs containing beta₂-adrenergics, UTIBRON NEOHALER should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using UTIBRON NEOHALER should not use another medicine containing a LABA for any reason. **Paradoxical Bronchospasm:** As with other inhaled medicines, UTIBRON NEOHALER can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with UTIBRON NEOHALER, it should be treated immediately with an inhaled, short-acting bronchodilator; UTIBRON NEOHALER should be discontinued immediately and alternative therapy instituted. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions have been reported after administration of indacaterol or glycopyrrolate, the components of UTIBRON NEOHALER. If signs suggesting allergic reactions

occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, UTIBRON NEOHALER should be discontinued immediately and alternative therapy instituted. UTIBRON NEOHALER should be used with caution in patients with severe hypersensitivity to milk proteins. **Cardiovascular Effects:** Indacaterol, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, UTIBRON NEOHALER may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore, UTIBRON NEOHALER should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. **Coexisting Conditions:** UTIBRON NEOHALER, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. **Worsening of Narrow-Angle Glaucoma:** UTIBRON NEOHALER should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** UTIBRON NEOHALER should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Hypokalemia and Hyperglycemia:** Beta₂-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility for cardiac arrhythmias. In 2 clinical trials of 12-weeks duration evaluating UTIBRON NEOHALER in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical practice of another drug and may not reflect the rates observed in clinical practice. The UTIBRON NEOHALER safety database included 2654 subjects with COPD in two 12-week lung function trials and one 52-week long-term safety study. A total of 712 subjects received treatment with UTIBRON NEOHALER 27.5 mcg/15.6 mcg twice daily (BID). The safety data described below are based on the two 12-week trials and the one 52-week trial. **12-Week Trials:** The incidence of adverse reactions associated with UTIBRON NEOHALER in Table 1 is based on two 12-week, placebo-controlled trials (Trials 1 and 2; N=1,001 and N=1,042 respectively). Of the 2040 subjects, 63% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 47 pack-years, with 52% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV₁) was 55% (range: 29% to 79%), the mean post-bronchodilator FEV₁/forced vital capacity (FVC) ratio was 50% (range: 19% to 71%), and the mean percent reversibility was 23% (range: 0% to 144%). The proportion of patients who discontinued treatment due to adverse reactions was 2.95% for the UTIBRON NEOHALER treated patients and 4.13% for placebo-treated patients.

Adverse Reaction	UTIBRON NEOHALER 27.5/15.6 mcg BID (N=508) n (%)	Indacaterol 27.5 mcg BID (N=511) n (%)	Glycopyrrolate 15.6 mcg BID (N=513) n (%)	Placebo (N=508) n (%)
Nasopharyngitis	21 (4.1)	13 (2.5)	12 (2.3)	9 (1.8)
Hypertension	10 (2.0)	5 (1.0)	3 (0.6)	7 (1.4)
Back pain	9 (1.8)	7 (1.4)	2 (0.4)	3 (0.6)
Oropharyngeal pain	8 (1.6)	4 (0.8)	8 (1.6)	6 (1.2)

Other adverse reactions occurring more frequently with UTIBRON NEOHALER than with placebo, but with an incidence of less than 1% include dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia. **52-Week Trial:** In a long-term safety trial, 614 subjects were treated for up to 52 weeks with indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg twice-daily, indacaterol/glycopyrrolate 27.5/31.2 mcg twice-daily or indacaterol 75 mcg once-daily. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the placebo-controlled trials of 12 weeks. Additional adverse reactions that occurred with a frequency greater than or equal to 2% in the group receiving indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg twice-daily that exceeded the frequency of indacaterol 75 mcg once-daily in this trial were upper and lower

ical Center and his associate. (Pediatrics. 2017;140[3]:e20170310)

In a retrospective cohort analysis, researchers found that just 2.5% of 2,568 hospitalized children with CAP who had a blood culture performed actually grew a pathogen. And of the detected pathogens, 82% were susceptible to penicillin. *Streptococcus pneumoniae* accounted for 78% of all

the pathogens that were found; it was detected in only 2% of all children who had blood cultures taken.

Just 11 children – or 0.43% of the children with a blood culture performed – had growth of a pathogen that was not treatable with penicillin, said lead author Mark Neuman, MD, director of research at Boston Children's Hos-

pital and his associates (Pediatrics. 2017;140[3]:e20171013).

The analysis was drawn from a cohort of 7,509 children hospitalized from 2007 to 2011, with children with complex chronic conditions excluded. Data for the analysis came from the Pediatric Health Information System Plus database, in which administrative, billing, laboratory,

and radiographic information is stored from six tertiary children's hospitals.

The investigators said that one challenge is that when blood cultures are drawn early in the course of evaluation and treatment, the severity of the child's CAP might not be apparent, which makes it difficult to know which children would benefit from a blood culture.

The routine performance of blood cultures in these children may not be indicated," Dr. Neuman and his associates said. "Researchers in future studies should seek to identify the clinical characteristics of children in whom obtaining blood cultures would lead to changes in clinical management, especially when identifying those patients at risk for CAP caused by organisms not susceptible to guideline-recommended, narrow-spectrum antibiotics."

Both studies were funded by the National Institutes of Health. For the physician exam study, additional funding was provided by individual grants from the Gerber Foundation, the National Center for Research Resources and the National Center for Advancing Translational Sciences, the National Institute for Allergy and Infectious Diseases and the National Institutes of Health, and a Trustee Award from Cincinnati Children's Hospital Medical Center. For the blood cultures study, individual researchers received funding from the National Institute of Allergy and Infectious Diseases and the Agency for Healthcare Research and Quality. For the physician exam study, no financial disclosures were reported. For the blood cultures study, Anne Blaschke, MD, PhD, reported receiving research funding from and other financial relationships with BioFire Diagnostics.

respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis. **Postmarketing Experience:** The following additional adverse reactions of angioedema and dyspnea have been identified during worldwide post-approval use of indacaterol/glycopyrrolate at higher than the recommended dose. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of indacaterol, a component of UTIBRON NEOHALER, may be potentiated. **Xanthine Derivatives, Steroids, or Diuretics:** Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta₂-adrenergic agonists such as indacaterol, a component of UTIBRON NEOHALER. **Non-Potassium-Sparing Diuretics:** The electrocardiographic (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as indacaterol, a component of UTIBRON NEOHALER, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of UTIBRON NEOHALER with non-potassium-sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc-Prolonging Drugs:** Indacaterol, one of the components of UTIBRON NEOHALER, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may have an increased risk of ventricular arrhythmias.

Beta-Blockers: Beta-adrenergic receptor antagonists (beta-blockers) and UTIBRON NEOHALER may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics: There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of UTIBRON NEOHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects. **Inhibitors of Cytochrome P450 3A4 and P-gp Efflux Transporter:** Drug interaction studies with indacaterol, a component of UTIBRON NEOHALER, were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil, and ritonavir). The data suggest that systemic clearance of indacaterol is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold area under the curve (AUC) increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Indacaterol was evaluated in clinical trials for up to 1 year at doses up to 600 mcg. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Therefore, no dose adjustment is warranted at the recommended 27.5/15.6 mcg twice-daily dose for UTIBRON NEOHALER when administered concomitantly with inhibitors of CYP3A4 and P-gp.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with UTIBRON NEOHALER or its individual components, indacaterol and glycopyrrolate, in pregnant women. Animal reproduction studies were conducted with individual components, indacaterol and glycopyrrolate. Because animal reproduction studies are not always predictive of human response, UTIBRON NEOHALER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physician if they become pregnant while taking UTIBRON NEOHALER. **Indacaterol:** Indacaterol was not teratogenic in Wistar rats and New Zealand rabbits at approximately 340 and 770 times, respectively, the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 1 mg/kg/day in rats and rabbits). **Glycopyrrolate:** Glycopyrrolate was not teratogenic in Wistar rats or New Zealand White rabbits at approximately 1400 and 530 times, respectively, the MRHD in adults (on an AUC basis at maternal inhaled doses up to 3.83 mg/kg/day in rats and up to 4.4 mg/kg/day in rabbits). **Non-teratogenic Effects: Indacaterol:** There were no effects on perinatal and postnatal developments in rats at approximately 110 times the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 0.3 mg/kg/day). **Glycopyrrolate:** There were no effects on perinatal and postnatal developments in rats at approximately 1100 times the MRHD in adults (on an AUC basis at maternal subcutaneous doses up to 1.88 mg/kg/day).

Labor and Delivery: There are no adequate and well-controlled human trials that have investigated the effects of UTIBRON NEOHALER during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, UTIBRON NEOHALER should be used during labor only if the potential benefit justifies the potential risk. In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrrolate, umbilical plasma concentrations were low. **Nursing Mothers: UTIBRON NEOHALER:** It is not known whether UTIBRON NEOHALER is excreted in human

breast milk. Because many drugs are excreted in human milk, caution should be exercised when UTIBRON NEOHALER is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of UTIBRON NEOHALER by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue UTIBRON NEOHALER, taking into account the importance of UTIBRON NEOHALER to the mother. **Indacaterol:** It is not known whether indacaterol is excreted in human breast milk. Indacaterol (including its metabolites) have been detected in the milk of lactating rats. **Glycopyrrolate:** It is not known whether glycopyrrolate is excreted in human breast milk. Glycopyrrolate (including its metabolites) have been detected in the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam. **Pediatric Use:** UTIBRON NEOHALER is not indicated for use in children. The safety and efficacy of UTIBRON NEOHALER in pediatric patients have not been established. **Geriatric Use:** Based on available data, no adjustment of UTIBRON NEOHALER dosage in geriatric patients is warranted. UTIBRON NEOHALER can be used at the recommended dose in elderly patients 75 years of age and older. Of the total number of subjects in clinical studies of UTIBRON NEOHALER, 45% were aged 65 and older, while 11% were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment:** Based on the pharmacokinetic characteristics of its monotherapy components, UTIBRON NEOHALER can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73 m²) or end-stage renal disease requiring dialysis, UTIBRON NEOHALER should be used if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrrolate may be increased in this population. **Hepatic Impairment:** Based on the pharmacokinetic characteristics of its monotherapy components, UTIBRON NEOHALER can be used at the recommended dose in patients with mild to moderate hepatic impairment. Studies in subjects with severe hepatic impairment have not been performed.

OVERDOSAGE: In COPD patients, doses of up to 600/124.8 mcg UTIBRON NEOHALER were inhaled over 2 weeks and there were no relevant effects on heart rate, QTc interval, blood glucose or serum potassium. There was an increase in ventricular ectopies after 14 days of dosing with 300/124.8 mcg and 600/124.8 mcg UTIBRON NEOHALER, but low prevalence and small patient numbers (N=49 and N=51 for 600/124.8 mcg and 300/124.8 mcg UTIBRON NEOHALER, respectively) precluded accurate analysis. In a total of four patients, non-sustained ventricular tachycardia was recorded, with the longest episode recorded being 9 beats (4 seconds). UTIBRON NEOHALER contains both indacaterol and glycopyrrolate; therefore, the risks associated with overdosage for the individual components described below apply to UTIBRON NEOHALER. Treatment of overdosage consists of discontinuation of UTIBRON NEOHALER together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage. **Indacaterol:** The potential signs and symptoms associated with overdosage of indacaterol are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, vomiting, drowsiness, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of indacaterol. In COPD patients, single doses of indacaterol 3000 mcg were associated with moderate increases in pulse rate, systolic blood pressure and QTc interval. **Glycopyrrolate:** An overdose of glycopyrrolate may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), constipation or difficulties in voiding. In COPD patients, repeated orally inhaled administration of glycopyrrolate at total doses of 124.8 mcg and 249.6 mcg once-daily for 28 days were well tolerated.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This study is important, because it included a large number of children. We have known for a long time that blood cultures are typically not helpful in older infants and children with CAP. The study also reminds me when educating residents and medical students that physical exam won't necessarily distinguish between bacterial vs viral pneumonias.



Can we stop worrying about the age of blood?

BY CHRISTOPHER L. CARROLL, MD, MS, FCCP

Blood transfusions are common in critically ill patients; two in five adults admitted to an ICU receive at least one transfusion during their hospitalization (Corwin HL, et al. *Crit Care Med.* 2004;32[1]:39). Recently, there has been growing concern about the potential dangers involved with prolonged blood storage. Several provocative observational and retrospective studies found that prolonged storage time (ie, the age of the blood being transfused) negatively affects clinical outcomes (Wang D, et al. *Transfusion.* 2012;52[6]:1184). But now, some newly published trials on blood transfusion practice, including one published in late September 2017 (Cooper DJ, et al. *N Engl J Med.* Published online, September 27, 2017) seem to debunk much of this literature. Was all of the concern about age of blood overblown?

The appeal of “fresh” blood is intuitive. As consumers, we’re conditioned that the fresher the better. Fresh food tastes best. Carbonated beverages go “flat” over time. The newest iPhone® device is superior to your old one. So, of course, it follows that fresh blood is also better for your health than older blood.

But, in order to have a viable transfusion service, blood has to be stored. Blood is a scarce resource, and blood banks need to keep an adequate supply on hand for expected clinical necessities, as well as for emergencies. Donors can’t be on standby, waiting in the hospital to provide immediate whole blood transfusion. Also, blood needs to be tested for infections and for potential interactions with the patient, and whole blood must be broken down into individual components for transfusion. All of this requires time and storage.

According to the US FDA, blood can safely be stored for up to 42 days, requiring that there be less than 1% hemolysis at the end of storage, and that more than 75% of the red blood cells remain

in circulation 24 hours after the transfusion. But some have suggested that these specifications aren’t comprehensive enough, citing studies that have linked prolonged storage to the development of “red blood storage lesion.” Red blood storage lesion has been theorized to have a variety of effects, including altered immunologic response and defective oxygen carrying capacity (Spinella PC, et al. *Transfusion.* 2011;51[4]:894). But do these changes have clinical implications?

In a randomized study of 100 critically ill adults supported by mechanical ventilation, 50 were randomized to receive “fresh” blood (median storage age 4 days, interquartile range 3-5 days) and 50 were randomized to receive “standard” blood (median storage age 26.5 days, interquartile range 21-36 days) (Kor DJ, et al. *Am J Respir Crit Care Med.* 2012;185[8]:842). The primary outcome was gas exchange, as prolonged storage of red blood cells could potentially lead to an increased inflammatory response in patients. However, the authors found no difference in gas exchange between the two groups, and there were no differences in immunologic function or coagulation status.

The ABLE (Age of Blood Evaluation) trial was a randomized, blinded trial of transfusion practices in critically ill patients (Lacroix J, et al. *N Engl J Med.* 2015;372:1410). In 64 centers in Canada and Europe, 2,430 critically ill adults were randomized to receive either “fresh” blood (mean storage age 6.1 ± 4.9 days) or “standard” blood (mean storage age 22.0 ± 8.4 days). The primary outcome was 90-day mortality, with a power of 90% to detect a 5% change in mortality between the two groups. The investigators found no statistically significant difference in 90-day mortality between the “fresh” and “standard” groups (37% vs 35.3%; hazard ratio 1.1; 95% CI 0.9 - 1.2). Additionally, there were no differences in secondary outcomes, including multiorgan system dysfunction, duration of supportive care, or development of nosocomial infections.



Dr. Carroll is Professor of Pediatrics, University of Connecticut, Division of Critical Care, Connecticut Children’s Medical Center, Hartford, Connecticut.

The INFORM (Informing Fresh versus Old Red Cell Management) trial was a randomized study of patients hospitalized in six centers in Canada, Australia, Israel, and the United States (Heddle NM, et al. *N Engl J Med.* 2016;375[2]:1937). A total of 24,736 patients received transfusions with either “fresh” blood (median storage age 11 days) or “standard” blood (median storage age 23 days). The primary outcome was in-hospital death, with a 90% power to detect a 15% lower relative risk. When comparing the 8,215 patients who received “fresh” blood and the 16,521 patients who received “standard” blood, the authors found no difference in mortality between the two groups (9.1% vs 8.8%; odds ratio 1.04; 95% CI 0.95 to 1.14). Furthermore, there were no differences in outcomes in the high-risk subgroups that included patients with cancer, patients in the ICU, and patients undergoing cardiovascular surgery.

A meta-analysis examined 12 trials of patients who received “fresh” blood compared with those who received “older” or “standard” blood (Alexander PE, et al. *Blood.* 2016;127[4]:400); 5,229 patients were included in these trials, in which “fresh” blood was defined as blood stored for 3 to 10 days and “older” blood was stored for longer durations. There was no difference in mortality between the two groups (relative risk 1.04; 95% CI 0.94 - 1.14), and no difference in adverse events (relative risk 1.02; 95% CI 0.91 - 1.14). However, perhaps surprisingly, “fresh” blood was associated with an increased risk of nosocomial infections (relative risk 1.09; 95% CI 1.00 - 1.18).

And finally, in the recently published TRANSFUSE trial (Cooper DJ, et al. *N Engl J Med.* Published online, September 27, 2017), 4,994 critically ill adults were randomized by 59 centers in five countries to receive transfusions stored for a short-term (median storage of 11 days) or long-term (median 21 days). Similar to the other three randomized trials, there was no difference in mortality between the two groups at both 90 and 180 days.

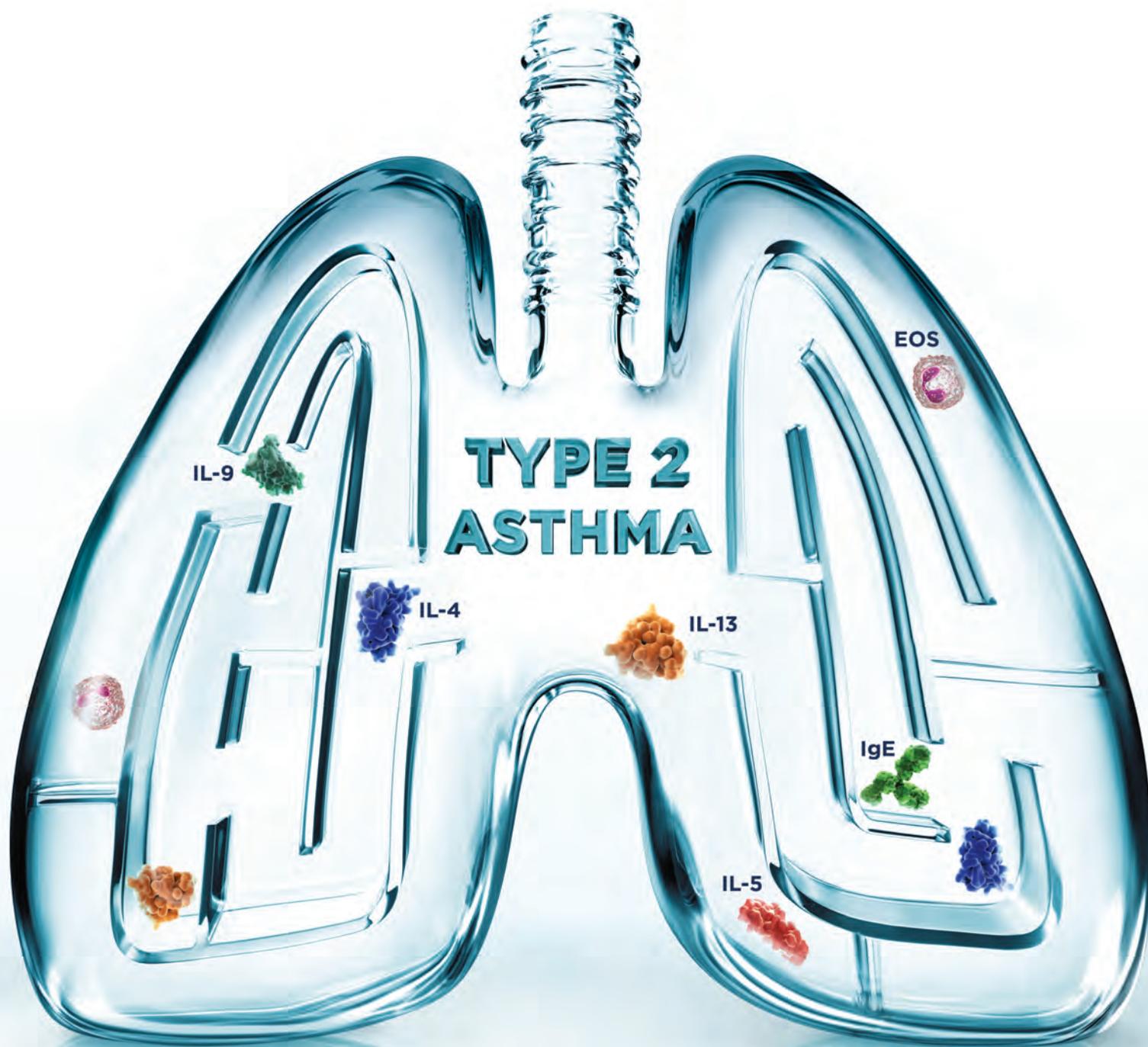
So, can we stop worrying about the age of the blood that we are about to transfuse? Probably. Taken together, these studies suggest that differences in the duration of red blood cell storage allowed within current US FDA standards aren’t clinically relevant, even in critically ill patients. At least, for now, the current practices for age of blood and duration of storage appear unrelated to adverse clinical outcomes.



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Transient tachypnea ups bronchiolitis risk

BY BRUCE JANCIN

Frontline Medical News

MADRID – A new Finnish study raises a provocative question: Is transient tachypnea of the newborn really transient?

Transient tachypnea of the newborn (TTN) has traditionally been viewed as a benign, self-limited condition involving 1-3 days of respiratory distress. But data from Finland's comprehensive national health

registries indicate that TTN in term babies is associated with significantly increased risk of subsequent bronchiolitis during infancy, Otto Helve, MD, reported at the annual meeting of the European Society for Paediatric Infectious Diseases.

"This association suggests similar pathogenic mechanisms in transient tachypnea of the newborn and bronchiolitis. We suggest that an intrinsic defect in sodium ion-driven

en pulmonary fluid transport may predispose to clinically significant bronchiolitis during the first year of life," said Dr. Helve, a pediatrician at the National Institute for Health and Welfare, Helsinki, and the University of Helsinki.

Of more than 1 million term babies born in Finland during 1996-2015, 17,569 were diagnosed with TTN. During the same period, 40,338 infants were hospitalized with a diagnosis of bronchiolitis attributable to respiratory syncytial virus infection.

In a multivariate analysis adjusted for birth year, gender, delivery method, gestational age, and parity, TTN was independently associated with a 1.2-fold increased risk of bronchiolitis during the first year of life.

Dr. Helve reported having no financial conflicts of interest regarding his study.

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Data from Finland's comprehensive national health registries indicate that transient tachypnea of the newborn in term babies is associated with significantly increased risk of subsequent bronchiolitis during infancy.

The odiferous thirdhand smoke residue, composed of tobacco-smoke toxins and known cancer-causing agents, adheres to house dust, furniture, carpets, walls, window glass, and other surfaces.

Thirdhand smoke shaping up as potential hazard

BY BRUCE JANCIN

Frontline Medical News

DENVER – Thirdhand smoke – the persistent residue that collects on indoor surfaces where people have smoked – is "clearly" a potentially hazardous exposure, John M. Rogers, PhD, said at the annual meeting of the Teratology Society.

Everyone knows about the hazards of secondhand smoke, which have led to widespread bans on smoking in public spaces. Still, the Centers for Disease Control and Prevention estimates that 58 million nonsmokers in the United

States are exposed to secondhand smoke on a regular basis. And where there is secondhand smoke, there is typically exposure to thirdhand smoke as well.

"If you walk into a hotel room you were told is a nonsmoking room and you take one breath and you know it's not nonsmoking, that's thirdhand smoke. Thirdhand smoke is all over the place where smokers have been," explained Dr. Rogers, director of the toxicity assessment division at the Environmental Protection Agency in Research Triangle Park, N.C.

Tobacco smoke contains thousands of chemicals. Among those

known to be harmful developmentally are nicotine, tobacco-specific nitrosamines, lead, cadmium, and various reactive molecules. The odiferous thirdhand smoke residue, composed of tobacco-smoke toxins and known cancer-causing agents, adheres to house dust, furniture, carpets, walls, window glass, and other surfaces. It's difficult to remove.

Unlike with secondhand smoke, ventilation won't do the job.

The main potential health risk is to young children, who ingest thirdhand smoke by the hand-to-mouth route and skin contact.

Thirdhand smoke is a much newer concept than secondhand smoke and has not yet actually been shown to pose a significant health risk. The term "thirdhand smoke" is still unfamiliar to many physicians and the general public. But that is likely to change.

Thirdhand smoke has become an area of intensive research interest, with California leading the way. The Tobacco-Related Disease Research Program, a state agency funded by a tax on the sale of tobacco products, has created a research consortium on thirdhand smoke, with studies underway investigating thirdhand smoke's precise chemical composition,

Continued on following page

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: In the old days, transient tachypnea of the newborn (TTN) was a diagnosis that didn't get much press. Now we know that children with primary ciliary dyskinesia have an increased incidence of TTN at birth and this registry reports a risk for future bronchiolitis. We clearly need to learn more about this neonatal respiratory disease!



E-cigarettes most popular among youngest adults

BY RICHARD FRANKI

Frontline Medical News

Over 15% of adults have used electronic cigarettes at some time, and about 3% reported current use when they were surveyed in 2016, according to the Centers for Disease Control and Prevention.

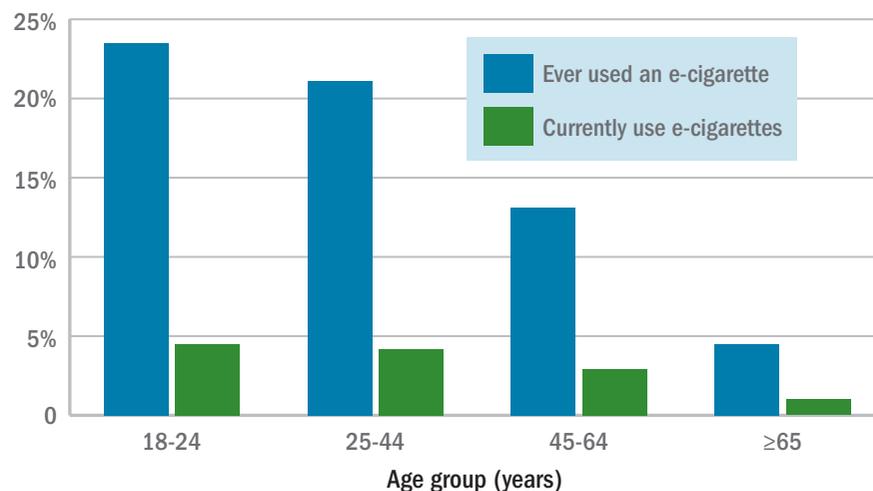
When those numbers are broken down by age group, the youngest adults are the most likely e-cigarette users: 23.5% of those aged 18-24 years had ever vaped and

4.5% were currently vaping either every day or on some days, the CDC reported (MMWR. 2017;66[33]:892).

For adults aged 25-44 years, ever use of e-cigarettes was 21.1% and current use was 4.2%, with adults aged 45-64 years at 13.1% and 2.9% and those aged 65 years and older checking in at 4.5% ever use and 1% current use, based on estimates derived from National Health Interview Survey data.

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Prevalence of e-cigarette use among adults by age, 2016



Note: Based on data from the National Health Interview Survey.

Source: MMWR. 2017;66(33):892

Continued from previous page

cytotoxicity, genotoxicity, and true impact on public health (www.trdrp.org).

Concern regarding thirdhand smoke's potential public health impact ramped up in response to a study in which investigators at the University of York (England) measured levels of various tobacco-specific nitrosamines, N-nitrosamines, and nicotine in house dust samples from the homes of smokers. The researchers estimated that years of early-life exposure to these compounds at the levels they detected could result in one excess case of cancer per 1,000 exposed individuals (Environ Int. 2014 Oct;71:139-47).

In addition to his update on thirdhand smoke, Dr. Rogers also touched on other recent tobacco-related developments, including a determination by the Food and Drug Administration that there has been no decline in tobacco use in the last 5 years in adolescents and young adults. While cigarette smoking by young people decreased, this was offset by a large increase in the use of electronic cigarettes and a smaller rise in the use of hookah tobacco. Indeed, e-cigarette use is now about double that of cigarettes among youth.

Also of concern is evidence of a striking socioeconomic disparity in smoking prevalence: Low-education, low-income Americans have far higher tobacco use rates.

"That's pretty alarming," he said. "I think a lot of people in this audience probably don't see a lot of smoking these days, but it's still around."

Dr. Rogers drew attention to updated evidence reviews on the reproductive and developmental effects of smoking contained in the U.S. Surgeon General's voluminous 2014 report on the health consequences of smoking. The report concluded that there is now sufficient evidence to infer a causal relationship between maternal smoking in pregnancy, ectopic pregnancy, and orofacial clefts. The available evidence is "suggestive but not sufficient" to infer causality between maternal smoking in pregnancy and atrial septal defects, clubfoot, gastroschisis, and attention-deficit/hyperactivity disorder and other disruptive behavior disorders.

Dr. Rogers reported having no financial disclosures related to his presentation, which he noted did not necessarily reflect the views and policies of the EPA.

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DIEGO_CEROVO/THINKSTOCK



Also of concern is evidence of a striking socioeconomic disparity in smoking prevalence: Low-education, low-income Americans have far higher tobacco use rates.

OVER 10,000 IPF PATIENTS HAVE BEEN TREATED WITH OFEV WORLDWIDE^{1,2}

SLOW THE PATH OF IPF PROGRESSION

OFEV (nintedanib) has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials³

DISCOVER MORE ABOUT OFEV INSIDE.

INDICATION AND USAGE

OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Hepatic Impairment

- OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.

FVC, forced vital capacity.

 **OFEV**[®]
(nintedanib)
capsules 150mg

TREAT NOW. SLOW PROGRESSION.



Respiratory infections linked to celiac disease

BY LORI LAUBACH

Frontline Medical News

The frequency of respiratory infections in the first 2 years of life could distinguish children who

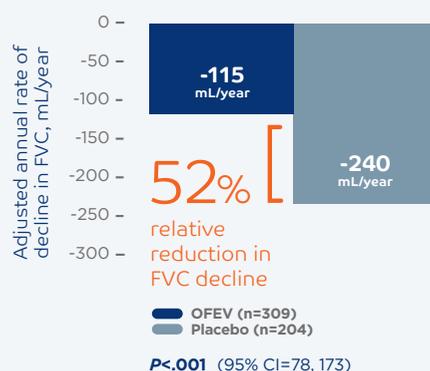
will develop celiac disease (CD) from those who will not in those with a family history of CD, according to Renata Auricchio, MD, University of Naples (Italy) Federico II, and her associates.

In a prospective cohort study, 373 newborns from families with at least one relative with CD were recruited. The cumulative incidence of new cases of CD was 6% at 3 years and 13.5% at 5 years of

age, the researchers noted. In the first year when no child produced anti-tissue transglutaminase (anti-tTG) antibodies, respiratory infections (upper and lower tract) were more common among the

OFEV has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials^{3*}

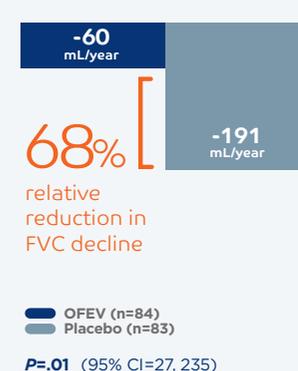
INPULSIS®-1 (Study 2)^{3,4}



INPULSIS®-2 (Study 3)^{3,4}



TOMORROW (Study 1)^{3,5}



CI, confidence interval.

*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.^{3,4}

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes

- OFEV (nintedanib) was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
- Conduct liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Monitor for adverse reactions and consider dosage modifications, interruption, or discontinuation as necessary for liver enzyme elevations.

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and <1% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.



ONE CAPSULE, TWICE DAILY WITH FOOD³

Not shown at actual size

case patients than among the controls (58% vs. 40%). During the second year, respiratory infections were again more frequent among the case patients than among controls (52% vs. 32%). And in the third year of life when most of the case patients were diagnosed with CD, no clinical event was more frequent in the case patients than

in the control group.

In a multivariate analysis, the researchers found that only respiratory infections in the second year of life were associated with a twofold increase in the risk of developing CD (odds ratio, 2.25; $P = .04$). The second variable was respiratory infections in the first year of life, which had a score of 1.58. Results

from the stepwise discriminant analysis suggested respiratory infections in the first and second years of life significantly contributed to the index of discrimination between the case patients and the controls.

“In this study, we report that early infections significantly contribute to the risk of developing CD,” Dr. Auricchio and her associates con-

cluded. “It is possible that the exposure to early infection stimulates a genetically predisposed immune profile, which contributes to the switch from tolerance to intolerance to gluten, which is a common food antigen.”

Read the full study in *Pediatrics* (doi: 10.1542/peds.2016-4102).

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3 out of every 10 patients on OFEV showed an improvement ($\leq 0\%$ decline) in lung function in the INPULSIS® trials³

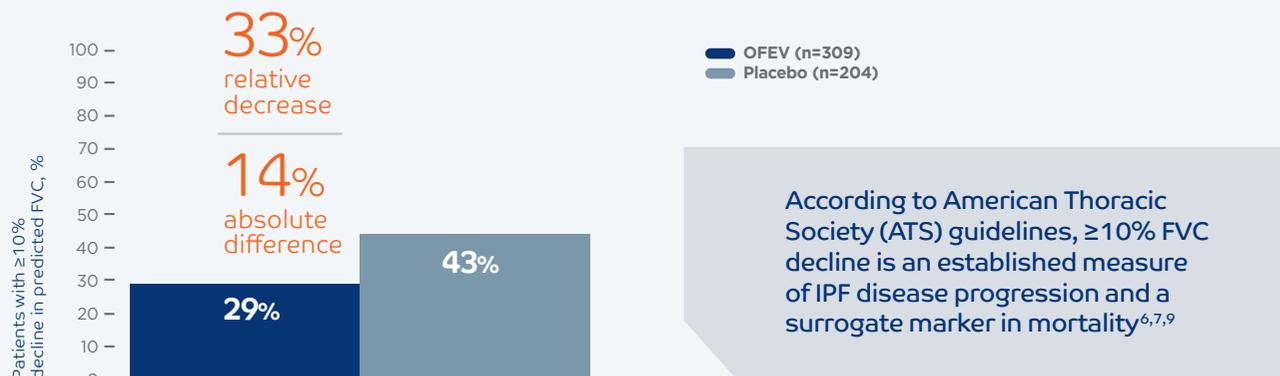
INPULSIS®-1³



- Similar results were observed in INPULSIS®-2³
- Lung function improvement is defined as a $\leq 0\%$ decline in predicted FVC at 52 weeks, meaning patients' predicted FVC increased from baseline³

LESS THAN ONE-THIRD OF PATIENTS ON OFEV HAD A MEANINGFUL DECLINE IN LUNG FUNCTION IN THE INPULSIS® TRIALS^{3,6-8}

INPULSIS®-1^{3,6-8}



- Similar results were observed in INPULSIS®-2³
- A meaningful decline is defined as patients with an absolute decline of ≥ 10 percentage points in predicted FVC at 52 weeks^{3,6-8}

In INPULSIS® trials, there was not a statistically significant difference in all-cause mortality for OFEV compared with placebo.³

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.



Hospital-led interventions cut hospitalizations

BY BIANCA NOGRADY

Frontline Medical News

Hospital-driven interventions designed to improve management of asthma in children achieved

significant reductions in monthly asthma-related hospitalizations and emergency department visits, according to a paper published online Sept. 18 in *JAMA Pediatrics*.

Long-term management of pe-

diatric asthma is challenging, and around 40% of children and adolescents hospitalized with the disease tend to be rehospitalized or revisit the emergency department within 12 months, according to Carolyn M.

Kercsmar, MD, of Children's Hospital Medical Center in Cincinnati, and her coauthors.

"Traditional care models do not adequately address underlying risk factors, propagating disparities

OFEV is only available through participating specialty pharmacies

TO GET YOUR APPROPRIATE PATIENTS WITH IPF STARTED ON OFEV:



CONDUCT liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)



COMPLETE the OFEV Prescription Form—available at www.OFEVhcp.com—and fax it to one of the participating specialty pharmacies



OFFER enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.
- The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.
- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

Please see accompanying brief summary of Prescribing Information, including Patient Information.

OFPROFISIFEB16

References: 1. Intercontinental Marketing Services (IMS) Health. Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. Accessed April 12, 2016. 2. Japan Drug NETwork (JD-NET). Data on file. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. Accessed April 12, 2016. 3. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016. 4. Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;370(22):2071-2082. 5. Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087. 6. Raghu G et al; on behalf of the ATS, ERS, JRS, and ALAT Committee on Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2011;183(6):788-824. 7. Richeldi L et al. *Thorax*. 2012;67(5):407-411. 8. du Bois RM et al. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. 9. Schmidt SL et al. *Chest*. 2014;145(3):579-585.



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and costly health care use,” they wrote (JAMA Pediatrics. 2017, Sep 18. doi: 10.1001/jamapediatrics.2017.2600).

This study, initiated by Cincinnati Children’s Hospital Medical Center, involved a range of interventions implemented with inpatients and outpatients and through the community setting, targeting the region’s

more than 36,000 children and adolescents with asthma, approximately 13,000 of whom were Medicaid insured.

These included a program that gave all patients a 30-day supply of medications, an asthma action plan, and standardized inhaler training; an asthma-specific history and physical examination form prompt-

ing assessment of chronic asthma control, severity, and triggers; a home health pathway of up to five in-home nurse visits; and care coordinators who applied interventions such as a risk assessment, education, medication home delivery, collaboration with a Medicaid managed care practitioner, and improved access to community resources.

Over the 5-year study, researchers saw a 41.8% relative reduction in asthma-related hospitalizations – from 8.1 to 4.7 per 10,000 Medicaid patients per month. Asthma-related visits to the ED decreased by 42.4%, from 21.5 to 12.4 per 10,000 Medicaid patients per month, and the percentage of

Continued on following page

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSE AND ADMINISTRATION: Testing Prior to OFEV Administration:

Conduct liver function tests and a pregnancy test prior to initiating treatment with OFEV [see Warnings and Precautions]. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily administered approximately 12 hours apart taken with food. **Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV [see Warnings and Precautions and Adverse Reactions]. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) [see Warnings and Precautions and Adverse Reactions]. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage. In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Hepatic Impairment:

Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment [see Use in Specific Populations]. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV [see Dosage and Administration]. **Elevated Liver Enzymes:** In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN [see Use in Specific Populations]. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders: Diarrhea:** Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifi-

cations or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV. **Nausea and Vomiting:** Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to treatment with OFEV [see Use in Specific Populations]. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations [see Warnings and Precautions]; Gastrointestinal Disorders [see Warnings and Precautions]; Embryo-Fetal Toxicity [see Warnings and Precautions]; Arterial Thromboembolic Events [see Warnings and Precautions]; Risk of Bleeding [see Warnings and Precautions]; Gastrointestinal Perforation [see Warnings and Precautions]. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials.

In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the pre-defined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain ^a	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation ^b	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous systemic disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension ^c	5%	4%

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

^b Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

^c Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant

patients rehospitalized or who returned to the ED for asthma within 30 days declined from 12% to 7%, “within 3 years of implementation of the inpatient care interventions,” the researchers noted.

There was also a significant increase in the percentage of patients discharged with a 30-day supply

of inhaled controller medications, from 50% in May 2008 to 90% in May 2010, and the percentage of patients discharged with a short course of oral corticosteroids increased from 0% to 70% by March 2011.

Outpatient processes ensured that Asthma Control Test scores were collected and that patients were

provided with asthma action plans. This was associated with an increase in the percentage of patients with well-controlled asthma from 48% to 54%.

“Implementation of an integrated, multilevel approach focused on enhancing availability and accessibility of treatments, removing barriers to adherence, mitigating risks

related to adverse exposures, and augmenting self-management and collaborative relationships between the family and the health care system was associated with improved asthma outcomes,” the authors wrote.

Noting that previous research has found 38%-70% of patients do not get their prescribed medications at hospital discharge, the authors said they believed giving a 30-day supply of all daily asthma medications at discharge was a key part of their success.

The study was supported by the Cincinnati Children’s Hospital Medical Center and one author received a grant from the National Institutes of Health. One author declared compensation for a committee role on a study of asthma treatments in children. No other conflicts of interest were declared.

use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose [see Data]. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%. **Data: Animal Data:** In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Lactation: Risk Summary:** There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats [see Data]. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV. **Data:** Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. **Females and Males of Reproductive Potential:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and

may reduce fertility in females of reproductive potential [see Use in Specific Populations]. Counsel patients on pregnancy prevention and planning. **Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV [see Dosage and Administration, Warnings and Precautions and Use in Specific Populations]. **Contraception:** Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. **Fertility:** Based on animal data, OFEV may reduce fertility in females of reproductive potential. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily [see Dosage and Administration]. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients [see Dosage and Administration]. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see Warnings and Precautions]. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

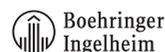
OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Patient Information). **Liver Enzyme and Bilirubin Elevations:** Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see Warnings and Precautions]. **Gastrointestinal Disorders:** Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see Warnings and Precautions and Adverse Reactions]. **Embryo-Fetal Toxicity:** Counsel patients on pregnancy prevention and planning. Advise females of reproductive potential of the potential risk to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV [see Warnings and Precautions and Use in Specific Populations]. **Arterial Thromboembolic Events:** Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see Warnings and Precautions]. **Risk of Bleeding:** Bleeding events have been reported. Advise patients to report unusual bleeding [see Warnings and Precautions]. **Gastrointestinal Perforation:** Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see Warnings and Precautions]. **Lactation:** Advise patients that breastfeeding is not recommended while taking OFEV [see Use in Specific Populations]. **Smokers:** Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. **Administration:** Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see Dosage and Administration].

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VIEW ON THE NEWS

Biopsychosocial model can improve pediatric asthma outcomes

Of importance, any future efforts to replicate this work in a patient-centered way should include consideration of how information on asthma management is communicated to and understood by patients. Standard tools such as asthma action plans often contain language and other information that is inaccessible to populations with low health literacy levels.

After years of elevated morbidity, the work of Kercksmar et al. is a demonstration of how interdisciplinary care focused within a biopsychosocial model can improve outcomes for vulnerable children. Future efforts to replicate these results in other communities should continue to emphasize this patient-centered, biopsychosocial philosophy, with heightened attention to the challenges that remain for children and families.

Sean M. Frey, MD, and Jill S. Halterman, MD, MPH, are in the department of pediatrics at the University of Rochester (N.Y.) School of Medicine and Dentistry. These comments are taken from an accompanying editorial (*JAMA Pediatrics*. 2017, Sep 18. doi: 10.1001/jamapediatrics.2017.2609). No conflicts of interest were declared.

FDA approves new therapy for COPD

Three COPD treatments are now available in one inhaler.

BY LUCAS FRANKI

Frontline Medical News

The Food and Drug Administration has approved Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol), a triple-therapy inhaler for the treatment of chronic obstructive pulmonary disease (COPD) in adult patients, according to a press release from GlaxoSmithKline and Innoviva.

Trelegy Ellipta combines an inhaled corticosteroid, a long-acting muscarinic antagonist, and a long-acting beta₂-adrenergic agonist into an inhaler meant for once-daily use in people with COPD. Chronic bronchitis and/or emphysema patients are also indicated for treatment. The FDA-approved dosage is 100 mcg of fluticasone furoate, 62.5 mcg of umeclidinium, and 25 mcg of vilanterol.

The most common adverse events associated with Trelegy

Ellipta include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis, and the inhaler is contraindicated for people with “severe hypersensitivity to milk proteins.” Trelegy Ellipta is not indicated for people with asthma or acute bronchospasm.

“This approval represents a significant therapeutic convenience for those appropriate patients already on Breo Ellipta, that require additional bronchodilation or for those patients already on a combination of Breo Ellipta and Incruse Ellipta,” Mike Aguiar, CEO of Innoviva said in the press release.

In results supporting the FDA approval, the IMPACT study, a 52-week phase 3 clinical trial including 10,355 COPD patients sponsored by GSK, found that patients receiving Trelegy Ellipta experienced a 25% reduction in moderate to severe exacerbations compared to patients receiving Anoro Ellipta,

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: For our Global Initiative for Chronic Obstructive Lung Disease 3 and 4 patients who have had hospitalizations, the prescription of multiple classes of inhaled medication is common. These patients are often receiving other medications, with complicated regimens. A patient’s medication list can become the time-schedule-map that consumes much of the day. This has significant impact on the patient’s life, finances, and the likelihood of compliance with medications. For those on triple therapy, the approval of this triple-therapy combination inhaler may offer hope for increased compliance with therapy.



and a 15% reduction in moderate to severe exacerbations, compared with patients receiving Relvar/Breo Ellipta. Change from baseline FEV₁, change from baseline scores on the St George’s Respiratory Questionnaire, and time to first moderate/severe COPD exacerbation also were improved in the Trelegy Ellipta study group compared to the others.

“This is the first study to report a comparison of a single inhaler triple therapy with two dual therapies, providing much needed clinical evidence about the ability of a single inhaler triple therapy to reduce exacerbations,” Patrick Vallance, president of R&D at GSK, noted in a press release announcing the results of the IMPACT study.

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Vaccine reduced risk for flu visits by 42%

BY MARY ANN MOON

Frontline Medical News

Last year’s influenza vaccination reduced the overall risk for flu-related medical visits by 42%, according to the Centers for Disease Control and Prevention.

In an article summarizing influenza activity in the United States during October 2016–May 2017, investigators said that most of the viral strains antigenically characterized at the CDC “were similar to the reference viruses representing the recommended components for the 2016-2017 vaccine.”

In addition, none of the thousands of samples tested showed resistance to the antivirals oseltamivir, zanamivir, and peramivir, said epidemiologist Lenee Blanton, MD, and her associates in the influenza division, National Center for Immunization and Respiratory Diseases in Atlanta.

The 2017-2018 influenza vaccine has been updated to include an additional influenza A (H1N1) component. This change was recommended by the Food and Drug Administration’s

Vaccines and Related Biological Products Advisory Committee, based on data from global influenza virologic and epidemiologic surveillance, genetic and antigenic characterization, human serology studies, antiviral susceptibility, and the availability of candidate influenza viruses (MMWR. 2017;66[25]:668-76).

Preliminary data show that, during the 2016-2017 flu season, there were 18,184 laboratory-confirmed, flu-related hospitalizations, for an overall incidence of 65 per 100,000 population, more than double that for the 2015-2017 season (31/100,000). Broken down by age groups, the rates per 100,000 population in this past season were 44 at ages 0-4 years, 17 at ages 5-17 years, 20 at ages 18-49 years, and 65 at ages 50-64 years, compared with 291 at ages 65 years and older. Finalized estimates of the number of influenza illnesses, medical visits, and hospitalizations averted by vaccination during the 2016-2017 season will be published in December, the investigators said.

Small study: Patients prefer microneedle flu vaccine

BY ELI ZIMMERMAN

Frontline Medical News

Influenza vaccinations given through a microneedle patch (MNP) received higher patient approval compared with traditional inoculation methods, according to a small study funded by the National Institutes of Health.

In a phase 1, randomized, placebo-controlled study, 100 patients between the ages of 18 and 49 years were split into four groups: one given the patch by a health care worker, one instructed to apply the patch at home, one given a vaccine through a traditional intramuscular injection, and one given a placebo.

Of those who took the patch, 70% (33 of 47) preferred the patch to intramuscular injection (The Lancet. 2017 Jun 27. doi: 10.1016/S0140-6736[17]30575-5).

All nonplacebo groups were given Fluvirin, the 2014-2015 licensed trivalent inactivated influenza vaccine, according to the researchers.

Protection against the virus 6 months after vaccination was similar across all groups other than the placebo group: 20-24 (83%-100%)

of 24 participants given the patch by a health care worker, 18-24 (75%-100%) of 24 in the group of patients who gave themselves the patch, and 20-25 (80%-100%) of 25 in the injection group having achieved seroprotection against the three influenza strains 6 months after vaccination.

When measuring reactogenicity, the investigators did find more patients (41 of 50) reported cases of pruritis in the microneedle group than in the injection group (4 of 25). However, these cases were mostly mild, while the injection group reported more grade 2 and grade 3 reactions, with grade 4 being the most severe.

There may also be potential for use among pediatric patients, who may be resistant to vaccinations because of the injection method, the researchers noted.

Some of the researchers are employees of Micron Biomedical, a company that manufactures microneedle products, and are listed as inventors on the licensed patents of these products. The investigators reported no other relevant financial disclosures.

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No increased mortality with readmission declines

BY SHARON WORCESTER

Frontline Medical News

Concerns that efforts to reduce 30-day hospital readmission rates under the Affordable Care Act's Hospital Readmission Reduction Program might lead to unintended increases in mortality rates appear to be unfounded, according to a review of more than 6.7 million hospitalizations for heart failure, acute myocardial infarction, or

pneumonia between 2008 and 2014.

In fact, reductions in 30-day readmission rates among Medicare fee-for-service beneficiaries are weakly but significantly correlated with reductions in hospital 30-day

mortality rates after discharge, according to Kumar Dharmarajan, MD, of Yale New Haven (Conn.) Health, and colleagues (JAMA. 2017 Jul 18;318[3]:270-8. doi: 10.1001/jama.2017.8444).

During the study period, a total of 2.96 million hospitalizations for heart failure, 1.2 million for acute MI, and 2.5 million for pneumonia were identified at 5,106 (heart failure), 4,772 (MI), and 5,057

VIEW ON THE NEWS

Time to reexamine, reengineer HRRP?

The findings by Dharmarajan and colleagues are "certainly good news," Karen E. Joynt Maddox, MD, wrote in an editorial.

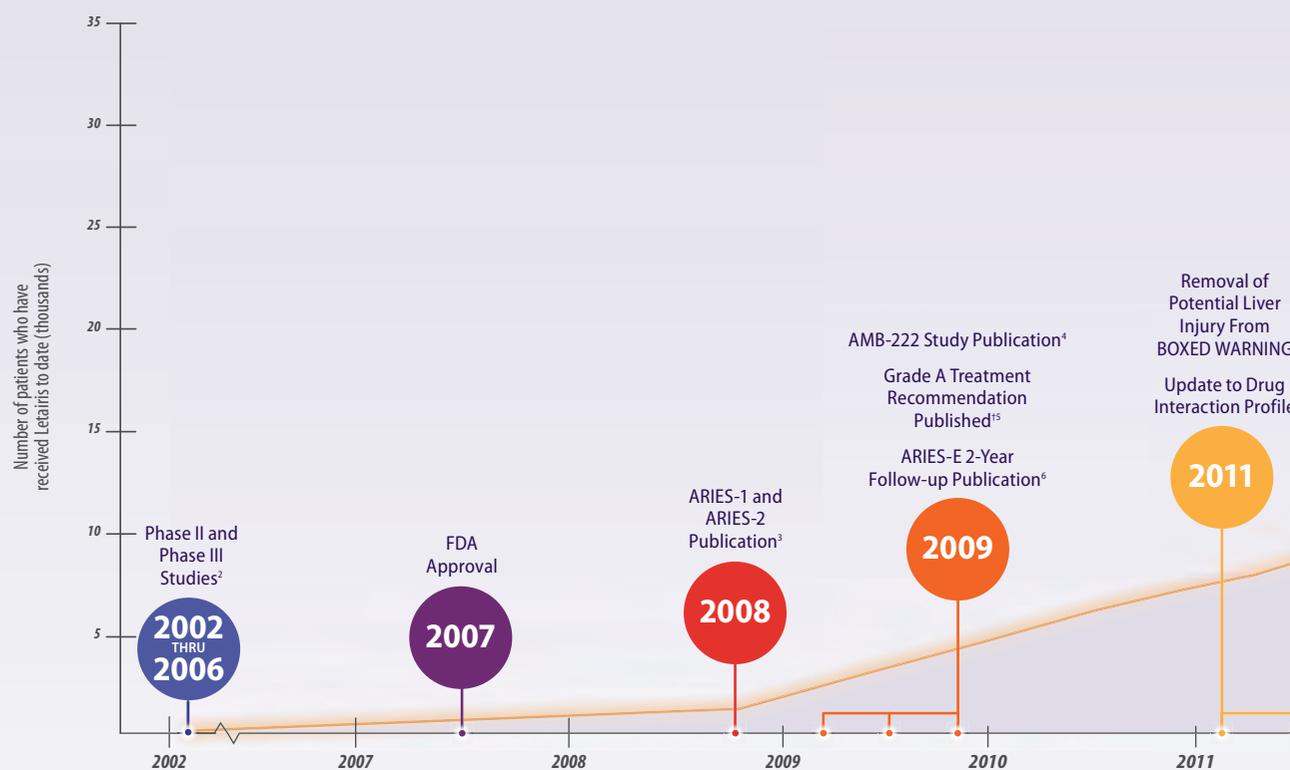
The study provides support for strategies that hospitals are using to reduce readmissions, and also underscores the importance of evaluating unintended consequences of policy changes such as the Affordable Care Act's Hospital Readmissions Reduction Program (HRRP), she said (JAMA. 2017 Jul 18;318[3]:243-4).

The study did not address the possibility that attention to reducing readmissions has taken priority over reducing mortality, which could have the unintended consequence of slowing improvements in mortality, she noted, suggesting that for this and other reasons it may be "time to reexamine and reengineer the HRRP to avoid unintended consequences and to ensure that its incentives are fully aligned with the ultimate goal of improving the health outcomes of patients.

"Only with full knowledge of the advantages and disadvantages of a particular policy decision can policy makers and advocates work to craft statutes and rules that maximize benefits while minimizing harms," she wrote.

Dr. Joynt Maddox is with Brigham and Women's Hospital, Boston. She is supported by a grant from the National Heart, Lung, and Blood Institute.

Confidence built from over a decade of clinical experience



*More than 35,000 patients have been prescribed Letairis since July 9, 2007. Based on LEAP database March 2017.²

†Based on PAH Evidence-Based Treatment Algorithm developed at the 4th World Symposium on Pulmonary Hypertension (February 2008), reflecting expert consensus on the available clinical data.¹⁰

#Based on PAH Evidence-Based Treatment Algorithm developed at the 5th World Symposium on Pulmonary Hypertension (February 2013), reflecting expert consensus on the available clinical data.¹¹

§Based on 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Class I Recommendation: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; is recommended/is indicated. Level of Evidence B: Data derived from a single randomized clinical trial or large non-randomized studies.⁸

Indication

Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- to improve exercise ability and delay clinical worsening
- in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability

Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Important Safety Information

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals
- Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment
- Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program

(pneumonia) short-term acute care hospitals, respectively. In January 2008, the mean hospital 30-day risk-adjusted readmission rates (RARRs) and risk-adjusted mortality rates (RAMRs) after discharge were 24.6% and 8.4% for heart failure, 19.3% and 7.6% for acute MI, and 18.3% and 8.5% for pneumonia, respectively, the investigators said.

From 2008 to 2014, the RARRs declined in aggregate across hospitals (-0.053% for heart failure, -0.044% for acute MI, and -0.033% for pneumonia).

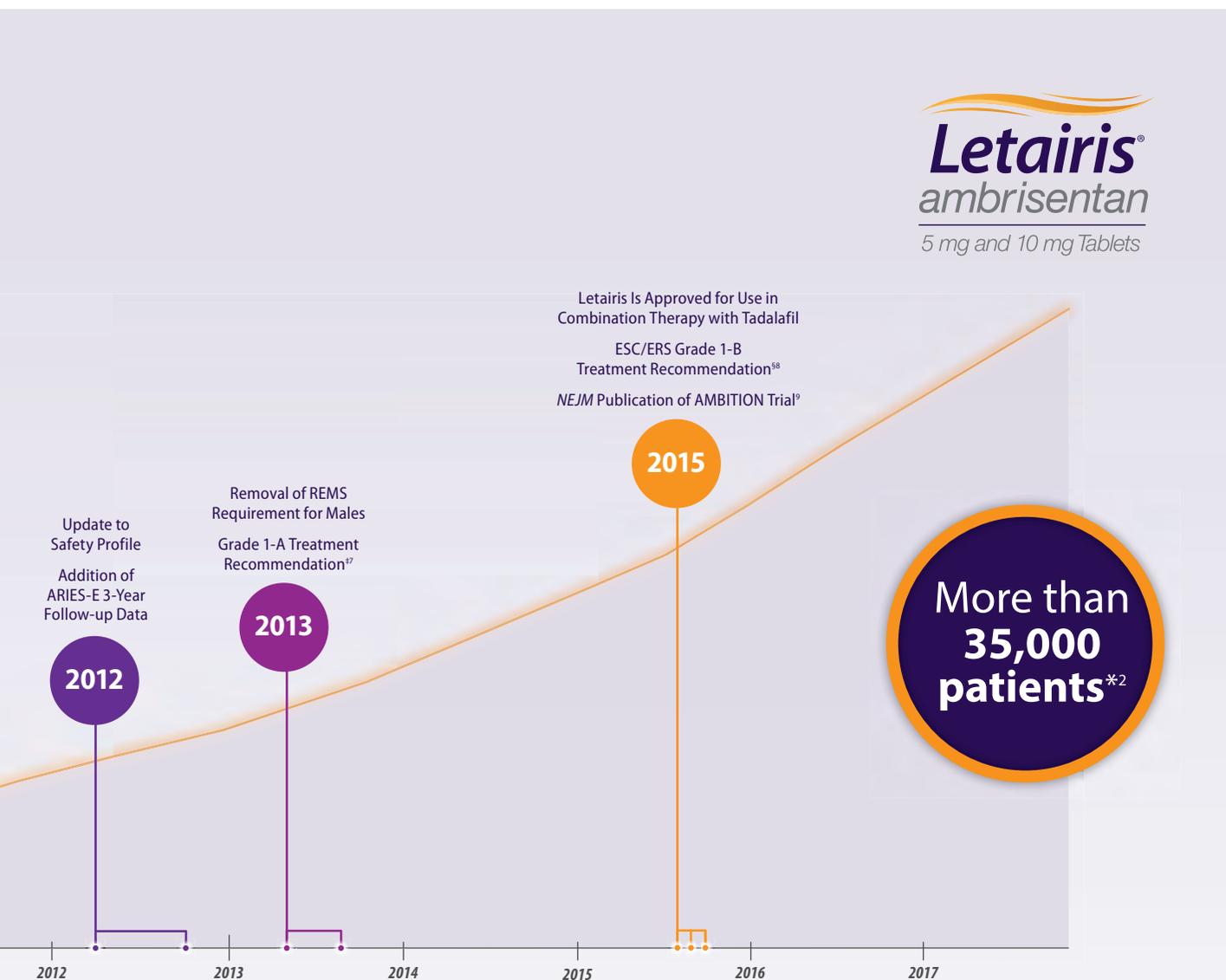
“In contrast, monthly aggregate trends across hospitals in 30-day risk-adjusted mortality rates after discharge varied by admitting condition” the investigators said.

For heart failure, acute MI, and pneumonia, there was an increase of 0.008%, a decrease of 0.003%, and an increase of 0.001%, respectively, they said.

The authors work under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures. Dr. Dharmarajan reported serving as a

consultant and scientific advisory board member for Clover Health at the time this research was performed. He is supported by grants from the National Institute on Aging and the American Federation for Aging Research, and the Yale Claude D. Pepper Older Americans Independence Center.

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Important Safety Information (continued)

Contraindications

- **Pregnancy:** Letairis can cause fetal harm
- **Idiopathic Pulmonary Fibrosis (IPF),** including IPF patients with pulmonary hypertension (WHO Group 3)

Warnings and Precautions

• Embryo-fetal toxicity and Letairis REMS Program requirements:

- Prescribers must be certified with the program by enrolling in and completing training
- All female patients, regardless of reproductive potential, must enroll in the Letairis REMS Program
- Male patients are not enrolled in the program
- Pharmacies must be certified with the program and must dispense to female patients who are authorized to receive Letairis

Further information is available at www.letairisrems.com or 1-866-664-5327.

• **Peripheral edema:** Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. Further evaluate patients who develop clinically significant fluid retention to determine the cause and possible need for edema treatment or to discontinue Letairis. In clinical studies, peripheral edema was more common with Letairis than with placebo (most edema was mild to moderate in severity); and with Letairis plus tadalafil than with either drug alone. There have also been postmarketing reports of fluid retention occurring within weeks after starting Letairis that required a diuretic, fluid management, or hospitalization for decompensating heart failure

• **Pulmonary edema with pulmonary veno-occlusive disease (PVOD):** Consider PVOD in patients who develop acute pulmonary edema during Letairis initiation and discontinue Letairis if PVOD is confirmed

• **Decreased sperm counts** have been observed in patients taking endothelin receptor antagonists and in animal fertility studies with ambrisentan. Counsel patients about potential effects on fertility

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

FDA tries to curtail abuse of 'orphan drug' program

BY SARAH JANE TRIBBLE,
KAISER HEALTH NEWS

The Food and Drug Administration is changing the way it approves orphan drugs after revela-

tions that drugmakers may be abusing a law intended to help patients with rare diseases.

In a blog post Sept. 12, FDA Commissioner Scott Gottlieb, MD, said he wants to ensure financial

incentives are granted "in a way that's consistent with the manner Congress intended" when the Orphan Drug Act was passed in 1983. That legislation gave drugmakers a package of incentives, including

tax credits, user-fee waivers, and 7 years of market exclusivity if they developed medicines for rare diseases.

A Kaiser Health News investigation published in January 2017

Important Safety Information (continued) Warnings and Precautions (continued)

- **Hematologic changes:** Measure hemoglobin prior to initiation of Letairis, at 1 month, and periodically thereafter. Letairis initiation is not recommended for patients with clinically significant anemia. Consider discontinuing Letairis if clinically significant decreases in hemoglobin occur and other causes have been excluded. Decreases in hemoglobin and hematocrit have been observed within the first few weeks of Letairis treatment, which may persist during treatment. There have also been postmarketing reports of anemia requiring transfusion

Adverse Reactions

- **Most common adverse reactions when used as monotherapy** compared to placebo were peripheral edema (17% vs 11%), nasal congestion (6% vs 2%), sinusitis (3% vs 0%) and flushing (4% vs 1%)
- **Most common adverse reactions in combination with tadalafil** compared to Letairis or tadalafil monotherapy were peripheral edema (45% vs 38% or 28%), headache (41% vs 34% or 35%), nasal congestion (19% vs 16% or 11%), cough (18% vs 13% or 16%), anemia (15% vs 7% or 11%), dyspepsia (11% vs 3% or 12%), and bronchitis (10% vs 4% or 9%)

Drug Interactions

- **Cyclosporine** increases ambrisentan exposure by 2-fold, limit Letairis to 5 mg once daily

Use in Specific Populations

- **Breastfeeding:** Choose Letairis or breastfeeding
- **Hepatic impairment:** Letairis is not recommended in patients with moderate or severe hepatic impairment. Fully investigate cause of liver injury in patients who develop hepatic impairment; discontinue Letairis if liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded

Dosage and Administration

- **Adult dosage:** Initiate Letairis 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, consider either increasing to Letairis 10 mg or tadalafil 40 mg. Do not split, crush, or chew tablets
- **Pregnancy testing:** Initiate Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment

References: 1. Letairis [package insert]. Foster City, CA: Gilead Sciences, Inc.; October 2015. 2. Data on file. Gilead Sciences, Inc. 3. Galie N, Olschewski H, Oudiz RJ, et al; for the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. *Circulation*. 2008;117(23):3010-3019. 4. McGoon MD, Frost AE, Oudiz RJ, et al. Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. *Chest*. 2009;135(1):122-129. 5. Barst RJ, Gibbs JSR, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1, suppl 5):S78-S84. 6. Oudiz RJ, Galie N, Olschewski H, et al; for the ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(21):1971-1981. 7. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25, suppl D):D60-D72. 8. Galie N, Humbert M, Vachiery JL, et al; 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J*. 2015;46:903-975. 9. Galie N, Barbera JA, Frost AE, et al; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373(9):834-844. 10. Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension: introduction. *J Am Coll Cardiol*. 2009;54(1, suppl 5):S1-S2. 11. Galie N, Simonneau G. The Fifth World Symposium on Pulmonary Hypertension. *J Am Coll Cardiol*. 2013;62(25, suppl D):D1-D3.

Letairis
ambrisentan
5 mg and 10 mg Tablets

Please see Brief Summary of full Prescribing Information, including **BOXED WARNING**, on the following page.

Letairis (ambrisentan) tablets, for oral use
Brief summary of full Prescribing Information.
See full Prescribing Information. Rx only.

WARNING: EMBRYO-FETAL TOXICITY
Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals [see *Contraindications, Warnings and Precautions, Use in Specific Populations*].
Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and one month after discontinuation of treatment [see *Dosage and Administration, Use in Special Populations*].
Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program [see *Warnings and Precautions*].

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening; and in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

DOSAGE AND ADMINISTRATION: See *Contraindications, Warnings and Precautions*, and *Use in Specific Populations* for additional information.

Adult Dosage: Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either increase Letairis to 10 mg or tadalafil to 40 mg, as needed and tolerated. Do not split, crush, or chew tablets.

Pregnancy Testing in Females of Reproductive Potential: Initiate treatment with Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment [see *Contraindications, Warnings and Precautions, Use in Specific Populations*].

CONTRAINDICATIONS: Pregnancy: Letairis may cause fetal harm when administered to a pregnant female. Letairis was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. [see *Warnings and Precautions, Use in Specific Populations*].

Idiopathic Pulmonary Fibrosis: Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group 3).

WARNINGS AND PRECAUTIONS: Embryo-fetal Toxicity and Letairis REMS Program: For all females, Letairis is available only through a restricted program called the Letairis REMS, because of risk of embryo-fetal toxicity [see *Contraindications, Warnings and Precautions, Use in Specific Populations*]. Notable requirements of the Letairis REMS program include that the Prescribers must be certified with the program by enrolling in and completing training. All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS. Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations*]. Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis. Further information is available at www.letairisrems.com or 1-866-664-5327.

Fluid Retention: Peripheral edema is a known class effect of endothelin receptor antagonists (ERAs), and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see *Adverse Reactions*]. Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients. In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy. Peripheral edema/fluid retention is more common with Letairis plus tadalafil than with Letairis or tadalafil alone.

Pulmonary Veno-occlusive Disease: If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed Letairis should be discontinued.

Decreased Sperm Counts: Decreased sperm counts have been observed in human and animal studies with another ERA and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility [see *Specific Populations*].

Hematological Changes: Decreases in hemoglobin concentration and hematocrit have followed administration of other ERAs and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks of treatment with Letairis, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12-week placebo-controlled studies was 0.8 g/dL. Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Letairis (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Letairis.

ADVERSE REACTIONS: See **BOXED WARNING** and *Warnings and Precautions* for additional serious adverse reactions.

found many drugs that now have orphan status aren't entirely new. Of about 450 drugs that have won orphan approval since 1983, more than 70 were drugs first approved by the FDA for mass-market use. Those include rosuvastatin (Crestor), aripiprazole (Abilify), and adalimumab (Humira), the world's best-selling drug.

Dr. Gottlieb announced plans to close a loophole that allows manufacturers to skip pediatric testing requirements when developing a common-disease drug for orphan use in children. He also signaled that bigger changes are being considered, announcing a public meeting to explore issues raised by scientific advances, such as the

increase in precision medicine and biologics.

"We need to make sure our policies take notice of all of these new challenges and opportunities," he wrote. Dr. Gottlieb, through his agency, declined multiple requests for interviews.

Over the years, drugmakers have fueled a boom in orphan drugs,

which often carry six-figure price tags. Nearly half of the new drugs approved by the FDA are now for rare diseases – even though many of them also treat and are marketed for common diseases.

Dr. Gottlieb became commissioner in May, a few months after three key Republican senators called for a federal investigation into potential abuses of the Orphan Drug Act, and the Government Accountability Office agreed to investigate.

The GAO has yet to begin its investigation, saying it doesn't expect to start work until late this year, when staff is available. Regardless, in late June, Dr. Gottlieb announced what would be the first in a series of updates that shift the way the FDA handles orphan drugs.

Those include:

- Eliminating a backlog in drug applications for orphan designation or status. Getting a designation is a critical first step if a company wants to win orphan incentives once the drug is approved for treatment use. And, much like the rise in approvals, the requests by companies to get drugs designated with orphan status has also skyrocketed. Dr. Gottlieb said in June that he wanted to get rid of the backlog; his blog post noted the effort was complete. About half of the 200 applications from drugmakers won orphan status.
- Mandating that drugmakers prove their medicine is clinically superior before getting the market exclusivity that comes with orphan drug status. The agency had lost a lawsuit in which a company said it was owed the exclusivity period regardless of whether its medicine was better. And two more lawsuits had been filed by Eagle Pharmaceuticals and United Therapeutics. The FDA Reauthorization Act, which passed in August, made it law that a drug has to be clinically superior to get the incentives.
- Closing the loophole for pediatric orphan drugs by requiring all drugs approved for common adult diseases, like inflammatory bowel disease, undergo pediatric testing when getting approval as a pediatric orphan drug. Pediatric testing is not required for orphan drugs, and Congress recently mandated that orphan drugs for cancer be tested for children. Still, the American Academy of Pediatrics celebrated the proposed change but warned it was only a first step. Bridgette Jones, MD, chair of American Academy of Pediatrics Committee on Drugs,

Clinical Trials Experience: Safety data for Letairis are presented from two 12-week, placebo-controlled studies (ARIES-1 and ARIES-2) in patients with PAH, and one randomized, double-blind, active-controlled trial in 605 patients with PAH (AMBITION) comparing Letairis plus tadalafil to Letairis or tadalafil alone. The exposure to Letairis in these studies ranged from 1 day to 4 years (N=357 for at least 6 months and N=279 for at least 1 year).

Use in Monotherapy: In ARIES-1 and ARIES-2, a total of 261 patients received Letairis at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3%

Adverse reaction	Placebo (N=132)		LETAIRIS (N=261)	
	n (%)	n (%)	n (%)	Placebo-adjusted (%)
Peripheral edema	14 (11)	45 (17)	6	
Nasal congestion	2 (2)	15 (6)	4	
Sinusitis	0 (0)	8 (3)	3	
Flushing	1 (1)	10 (4)	3	

Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously. The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for Letairis (5%; 13/261 patients). During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Use in Combination with Tadalafil: The mean exposure to Letairis + tadalafil in the AMBITION study was 78.7 weeks. The adverse reactions that occurred in >5% more patients receiving Letairis + tadalafil than receiving Letairis or tadalafil monotherapy in AMBITION are shown in Table 2.

Table 2 Adverse Reactions Reported More Commonly (>5%) on Letairis + Tadalafil than on Letairis or Tadalafil Monotherapy in AMBITION

Adverse Reactions	Letairis + Tadalafil Combination Therapy (N=302) n (%)	Letairis Monotherapy (N=152) n (%)	Tadalafil Monotherapy (N=151) n (%)
Peripheral edema	135 (45)	58 (38)	43 (28)
Headache	125 (41)	51 (34)	53 (35)
Nasal congestion	58 (19)	25 (16)	17 (11)
Cough	53 (18)	20 (13)	24 (16)
Anemia	44 (15)	11 (7)	17 (11)
Dyspepsia	32 (11)	5 (3)	18 (12)
Bronchitis	31 (10)	6 (4)	13 (9)

Peripheral edema was more frequent on combination therapy; however, there was no notable difference observed in the incidence of peripheral edema in elderly patients (≥65 years, 37%) versus younger patients (<65 years, 39%) on combination therapy or Letairis monotherapy in AMBITION. Treatment discontinuations due to adverse events while on randomized treatment were similar across treatment groups: 16% for Letairis + tadalafil, 14% for Letairis alone, and 13% for tadalafil alone.

Use in Patients with Prior ERA Related Serum Liver Enzyme Abnormalities: In an uncontrolled, open-label study, 36 patients who had previously discontinued ERAs (bosentan, an investigational drug, or both) due to aminotransferase elevations >3x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5x ULN, but 9 patients had elevations >8x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with readministration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

Consult the full Prescribing Information for additional information regarding adverse reactions, including postmarketing events.

DRUG INTERACTIONS: Multiple dose coadministration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine.

USE IN SPECIFIC POPULATIONS: Pregnancy Category X: Risk Summary: Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications, Warnings and Precautions]. Animal Data: Letairis was teratogenic at oral doses of ≥15 mg/kg/day (AUC 51.7 h-µg/mL) in rats and ≥7 mg/kg/day (24.7 h-µg/mL) in rabbits; it was not studied at lower doses. These doses are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h-µg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard

and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (on a mg/m² body surface area basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage of 17x the human dose based on mg/m². **Nursing Mothers:** It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Letairis, a decision should be made whether to discontinue nursing or discontinue Letairis, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of Letairis in pediatric patients have not been established. **Geriatric Use:** In the two placebo-controlled clinical studies of Letairis, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with Letairis than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

Females and Males of Reproductive Potential: Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and one month after stopping treatment with Letairis. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options [see BOXED WARNING and Dosage and Administration]. **Contraception:** Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine device (IUD), contraceptive implant, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see BOXED WARNING]. **Infertility: Males:** In a 6-month study of another ERA, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data from ERAs, it cannot be excluded that ERAs such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility [see Warnings and Precautions].

Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan. Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. **Elevation of Liver Transaminases:** Other ERAs have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure [see Adverse Reactions]. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

OVERDOSAGE: There is no experience with overdosage of Letairis. The highest single dose of Letairis administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention.

GS22-081-015-PI October 2015



For detailed information, please see full Prescribing Information. To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com. Manufactured and marketed by: Gilead Sciences, Inc., Foster City, CA 94404, USA ©2017 Gilead Sciences, Inc. All rights reserved. LETP0520 08/17 Letairis, the Letairis logo, GILEAD and the GILEAD logo are registered trademarks of Gilead Sciences, Inc., or its related companies. Other brands noted herein are the property of their respective owners.



Medicare payments may be lower than promised

BY GREGORY TWACHTMAN

Frontline Medical News

Physicians will likely see a 0.31% uptick in their Medicare payments in 2018 and not the 0.5% promised in the Medicare Access and CHIP Reauthorization Act.

Officials at the Centers for Medicare & Medicaid Services were not able to find adequate funding in so-called misvalued codes to support the larger increase, as required by law, according to the proposed Medicare physician fee schedule for 2018.

CMS also failed to hit its misvalued code target in 2016, resulting in a 0.18% across-the-board reduction to the physician fee schedule in 2017 instead of the statutorily promised 0.5% increase.

Other provisions in the proposed Medicare physician fee schedule may be more palatable than the petite pay raise.

The proposal would roll back data reporting requirements of the Physician Quality Reporting System (PQRS), to better align them with the new Quality Payment Program (QPP), and will waive half of penalties assessed for not meeting PQRS requirements in 2016.

“We are proposing these changes based on stakeholder feedback and to better align with the MIPS [Merit-Based Incentive Payment System track of the QPP] data submission requirements for the quality performance category,” according to a CMS fact sheet on the proposed fee schedule.

“This will allow some physicians who attempted to report for the 2016 performance period to avoid penalties and better align PQRS with MIPS as physicians transition to QPP,” officials from the American College of Physicians said in a statement.

Other physician organizations said they believed the proposal did not go far enough.

“While the reductions in penalties represent a move in the right direction, the [American College of Rheumatology] believes CMS should establish a value modifier adjustment of zero for 2018,” ACR officials said in a statement. “This would align with the agency’s policy to ‘zero out’ the impact of the resource use component of the Merit-based Incentive Payment System in 2019, the successor to the value modifier program. This provides additional time to continue refining the cost measures and gives physicians more time to understand the program.”

The proposed fee schedule also would delay implementation of the appropriate use criteria (AUC) for imaging services, a program that would deny payments for imaging services unless the ordering physician consulted the appropriate use criteria.

The American Medical Association “appreciates CMS’ decision to postpone the implementation of this requirement until 2019 and to make the first year an opportunity for testing and education where consultation would not be required as a condition of payment for imaging services,” according to a statement.

“We also applaud the proposed delay in implementing AUC for diagnostic imaging studies,” ACR said in its statement. “We will be gauging the readiness of our members to use clinical support systems. ... We support simplifying and phasing-in the program requirements. The ACR also strongly supports larger exemptions to the program,” such as physicians in small groups and rural and underserved areas.

‘While the reductions in penalties represent a move in the right direction, the [American College of Rheumatology] believes CMS should establish a value modifier adjustment of zero for 2018.’

The proposed fee schedule also seeks feedback from physicians and organizations on how Medicare Part B pays for biosimilars. Under the 2016 fee schedule, the average sales prices (ASPs) for all biosimilar products assigned to the same reference product are included in the same CPT code,

meaning the ASPs for all biosimilars of a common reference product are used to determine a single reimbursement rate.

That CMS is looking deeper at this is being seen as a plus.

Biosimilars “tied to the same reference product may

not share all indications with one another or the reference product [and] a blended payment model may cause significant confusion in a multitiered biosimilars market that may include both interchangeable and noninterchangeable products,” the Biosimilars Forum said in a statement. The current situation “may lead to decreased physician confidence in how they are reimbursed and also dramatically reduce the investment in the development of biosimilars and thereby limit treatment options available to patients.”

Both the Biosimilars Forum and the ACR support unique codes for each biosimilar.

“Physicians can better track and monitor their effectiveness and ensure adequate pharmacovigilance in the area of biosimilars” by employing unique codes, according to ACR officials.

The fee schedule proposal also would expand the Medicare Diabetes Prevention Program (DPP), currently a demonstration project, taking it nationwide in 2018. The

proposal outlines the payment structure and supplier enrollment requirements and compliance standards, as well as beneficiary engagement incentives.

Physicians would be paid based on performance goals being met by patients, including meeting certain numbers of service and maintenance sessions with the program as well as achieving specific weight-loss goals. For beneficiaries who are able to lose at least 5% of body weight, physicians could receive up to \$810. If that weight-loss goal is not achieved, the most a physician could receive is \$125, according to a CMS fact sheet. Currently, DPP can only be employed via office visit; however, the proposal would allow virtual make-up sessions.

“The new proposal provides more flexibility to DPP providers in supporting patient engagement and attendance and by making performance-based payments available if patients meet weight-loss targets over longer periods of time,” according to the AMA.

The fee schedule also proposes more telemedicine coverage, specifically for counseling to discuss the need for lung cancer screening, including eligibility determination and shared decision making, as well as psychotherapy for crisis, with codes for the first 60 minutes of intervention and a separate code for each additional 30 minutes. Four add-on codes have been proposed to supplement existing codes that cover interactive complexity, chronic care management services, and health risk assessment.

For clinicians providing behavioral health services, CMS is proposing an increased payment for providing face-to-face office-based services that better reflects overhead expenses.

Comments on the fee schedule update were due Sept. 11. The final rule is expected in early November.

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Continued from previous page

said Sept. 12 that orphan drugs are “still mostly exempt from pediatric study requirements ... children deserve access to safe, effective medications.”

Martin Makary, MD, who wrote a critical 2015 paper on orphan approvals, said the changes at the agency indicate that Dr. Gottlieb seems “concerned about all the right things. The government does a lot of lip service in general. This is not lip service.”

The restructuring has been swift in some ways.

Sandra Heibel, PhD, a senior consultant at Haffner Associates, a firm that helps companies

submit orphan drug applications, noted that the approval process for designations definitely sped up over the summer, and “we are absolutely getting responses from the FDA back in 90 days. That has come through.”

Other changes to the agency, though, will evolve slowly. For example, the orphan drug office has begun reaching across the FDA’s divisions for help in reviewing drugs. In May, the FDA’s orphan reviews began to work with the office of pediatric therapeutics to review pediatric applications – ideally increasing the expertise applied when considering a company’s request for orphan drug use in children.

In an interview, FDA confirmed that Dr. Gottlieb’s orphan modernization plan is part of a larger effort to increase competition and decrease drug prices. One focus is on targeted drugs – especially those that affect rare diseases or diseases for which there is no effective therapy, the agency said.

“Such drugs present some of the biggest opportunities in medicine to treat and cure debilitating and very costly diseases,” the agency stated.

Kaiser Health News is a national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.

Hurricane Harvey tests hospital teams' mettle

BY ELI ZIMMERMAN

Frontline Medical News

As Houston-area citizens evacuated or hunkered down at home in anticipation of Hurricane Harvey, doctors like Mary L. Brandt, MD, packed a bag and headed to work.

"I came in on Saturday morning [Aug. 23] – I was on call – and so I packed a big suitcase and a big bag of food because I anticipated I would be here until Thursday," Dr. Brandt said in an interview, "So I became part of the 'ride-out crew.'"

Hospitals were hit hard by Hurricane Harvey, and many struggled against the effects of the Category 4 storm, which made landfall then stalled over Texas for almost a week, pummeling the area.

Preparations began well before the hurricane arrived. As weather experts and government officials warned of the storm's imminent arrival, Houston's Texas Children's Hospital wasted no time making necessary plans in addition to the safeguards their facilities already had in place, Dr. Brandt said.

"We all know this [flooding] could happen, so all the facilities in the medical center have flood gates, and generators are out of the basement so that there is not any risk of losing all electricity, but then the issue becomes the staff," Dr. Brandt said. "They can't get to and from the facility, and that's particularly true if they live in the periphery of Houston, which is common."

The situation was the same for many area hospitals. Just 2 miles away from Texas Children's Hospital, SreyRam Kuy, MD, associate chief of staff at the Michael E. DeBakey VA Medical Center, and her colleagues prepared to run the hospital with a skeleton crew.

"We were preparing when it was still a tropical storm, and we talked to the staff ahead of time to let them know this would be a marathon, not a sprint," Dr. Kuy said in an interview. "We had people staying in the hospital ahead of time because we were worried that when the hurricane hit, we would not be able to have people return."

But when Harvey made landfall with Category 4 intensity, many medical facilities were caught by surprise.

"We didn't know how bad it would be, I honestly don't think anyone in the city or the state had any idea of how tremendous the impact would

be, particularly with the flooding," Dr. Kuy said. "We had staff going 5, 6 days here at the hospital, working continuously, sleeping on the floor, and because of that, we were able to perform multiple emergency sur-

geries during the disaster, including laparoscopic treatment of ruptured appendicitis and replacement of an infected aortic graft, which required massive transfusion." The VA hospital broke from its core mission of

caring for veterans, treating "homeless folks and nonveterans who were brought here by the Coast Guard, or the ambulances, or by air."

At Texas Children's Hospital, Dr.

Continued on page 34

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INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
 - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
 - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
 - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS.

Eliquis[®]

(apixaban) tablets 5mg
2.5mg

ELIQUIS for initial DVT/PE treatment*—

And for appropriate patients, continue on a low dose[†] to reduce the risk of recurrent DVT/PE following initial therapy¹



To learn more about ELIQUIS, visit

hcp.eliquis.com



*Initial therapy: 10 mg, orally twice daily for the first 7 days. After 7 days, 5 mg orally twice daily.

[†]Extended therapy: 2.5 mg, orally twice daily. **Please see full dosing information in the Prescribing Information.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Reference: 1. ELIQUIS[®] Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.

Please see Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on adjacent pages.

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Bristol-Myers Squibb



ELIQUIS® (apixaban) tablets, for oral use

Rx ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see *Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1)* in full Prescribing Information].

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of ELIQUIS and neuraxial procedures is not known

[see *Warnings and Precautions*]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [see *Warnings and Precautions*].

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated [see *Warnings and Precautions*].

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation—ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery—ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding [see *Warnings and Precautions and Adverse Reactions*]
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) [see *Adverse Reactions*]

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see *Dosage and Administration (2.4)* and *Clinical Studies (14.1)* in full Prescribing Information].

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding [see *Dosage and Administration (2.1)* in full Prescribing Information and *Adverse Reactions*].

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) [see *Drug Interactions*].

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse the bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies [see *Clinical Pharmacology (12.2)* in full Prescribing Information]. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration [see *Overdosage*].

Hemodialysis does not appear to have a substantial impact on apixaban exposure [see *Clinical Pharmacology (12.3)* in full Prescribing Information]. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS (apixaban) have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation [see *Warnings and Precautions*]
- Bleeding [see *Warnings and Precautions*]
- Spinal/epidural anesthesia or puncture [see *Warnings and Precautions*]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies [see *Clinical Studies (14)* in full Prescribing Information], including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

† Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

‡ Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

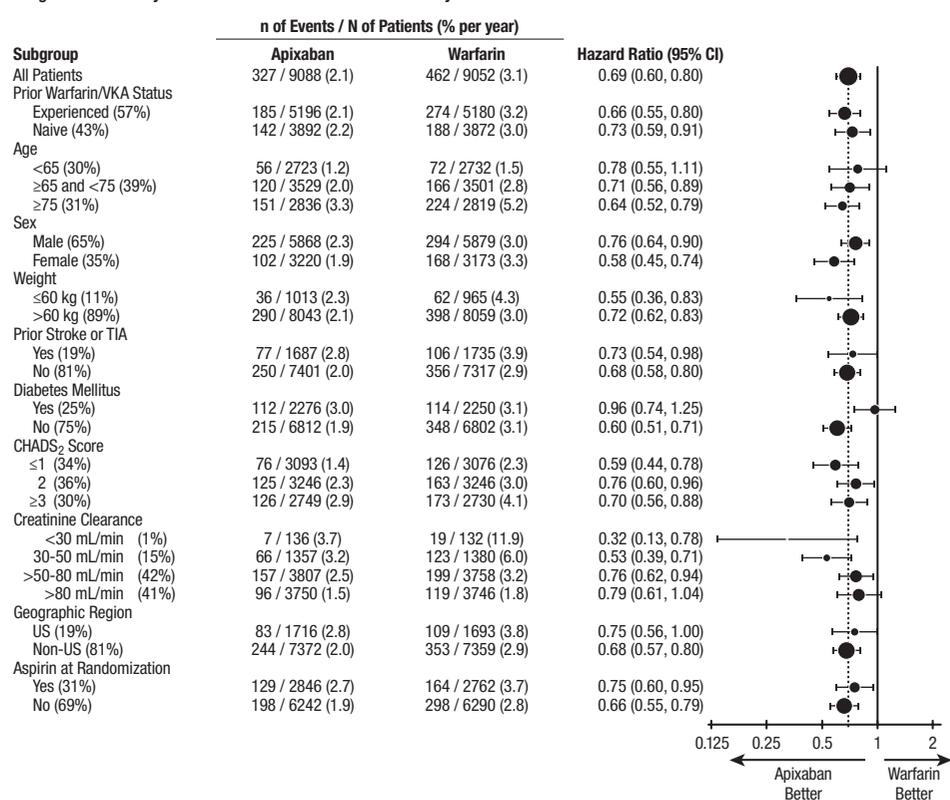
§ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

¶ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

** GI bleed includes upper GI, lower GI, and rectal bleeding.

†† Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, CHADS₂ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)* in full Prescribing Information].

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp [see *Dosage and Administration (2.5)* and *Clinical Pharmacology (12.3)* in full Prescribing Information].

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban [see *Clinical Pharmacology (12.3)* in full Prescribing Information].

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting [see *Warnings and Precautions*].

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics [see *Dosage and Administration (2.1)* in full Prescribing Information]:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose [see *Dosage and Administration (2.1)* in full Prescribing Information] will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study [see *Clinical Pharmacology (12.3)* in full Prescribing Information]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis [see *Dosage and Administration (2.1)* in full Prescribing Information].

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Fxa activity) data in subjects with ESRD maintained on dialysis [see *Clinical Pharmacology (12.3)* in full Prescribing Information].

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided [see *Clinical Pharmacology (12.2)* in full Prescribing Information]. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) [see *Clinical Pharmacology (12.2)* in full Prescribing Information].

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding [see *Warnings and Precautions*].

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (*Medication Guide*).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas [see *Warnings and Precautions*]. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see *Use in Specific Populations*].
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube [see *Dosage and Administration (2.6)* in full Prescribing Information].
- What to do if a dose is missed [see *Dosage and Administration (2.2)* in full Prescribing Information].

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The National Guard Malcolm McClendon/Texas Military



Continued from page 29

Brandt and her colleagues were dealing with similar situations, staying on their feet and moving quickly as rescued patients arrived by air.

“We were near the area that was flooding really terribly, and so the Coast Guard had been coming in and bringing kids,” Dr. Brandt said. “Sometimes, we knew what was coming and sometimes we didn’t. It was pretty much controlled chaos.”

Staff shared responsibilities, often taking on tasks far outside their usual roles.

“We didn’t have enough people working the cafeteria, and so, at one point, I put on my hair net, grabbed a ladle, and served in the lunch line,” Dr. Kuy said.

Throughout the storm and flooding, medical professionals fought through exhaustion and depleting supplies, all with little or no knowledge of how their own homes and families were faring.

“We had people here for so long, and they had no idea what was happening in their own homes,” Dr. Kuy said. “They were watching on the news, seeing the reports and watching their own neighborhoods flooded.”

Dr. Brandt and her colleagues would watch as reports came in of what was happening beyond the hospital walls.

“We have some meeting areas, we would watch the weather together and that goes from the janitors to the head of the hospital who was in the hospital with us,” she said.

Despite the chaos outside, morale did not waiver for either Dr. Kuy’s or Dr. Brandt’s crew.

“I remember walking throughout the hospital, doing my rounds, checking up on the units. I went to talk with some of the staff nurses,

and what struck me was as I walk in I see these big smiles on their faces; I absolutely did not expect that,” Dr. Kuy said. “They had been in the hospital for 5 days; they were exhausted. It just makes me so proud to serve along these kinds of people.”

As travel became possible, Dr. Kuy and other area physicians – as well as volunteers from across the country – began to shift their focus to evacuation shelters, treating ambulatory patients there.

“The response has been phenomenal,” said Dr. Kuy. “I met an ER doctor from North Carolina who came to volunteer, we have FEMA [Federal Emergency Management Agency] doctors from all across the state, and then of course, all the people from the different VA [hospitals].”

Pediatricians have sent their support as well, offering time and supplies to help take care of the patients at Texas Children’s Hospital, Dr. Brandt said.

At presstime, volunteers were still needed. The Texas Department of State Health Services opened a web portal for volunteer opportunities, and lifted restriction on out-of-state doctors from practicing medicine without state registration.

While there is still much that needs to be done to recover, those on the ground said that they feel an overwhelming feeling of community as people face what will inevitably be a tough road ahead.

“Houston has a reputation and a culture of helping neighbors and it has been astounding to watch what’s happening,” said Dr. Brandt. “No matter how tired people are or how stressful any cases are, everyone’s morale stays high.”

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Health IT: Cybercrime risks are real

BY ELI ZIMMERMAN

Frontline Medical News

Aging equipment, valuable data, and an improperly trained workforce make health care IT extraordinarily vulnerable to external malfeasance, as demonstrated by the WannaCry virus episode that occurred this spring in the United Kingdom.

Computer hackers used a weakness in the operating system employed by the U.K. National Health Service, allowing the WannaCry virus to spread quickly across connected systems. The ransomware attack locked clinicians out of patient records and diagnostic machines that were connected, bringing patient care to a near standstill.

The attack lasted 3 days until Marcus Hutchins, a 22-year-old security researcher, stumbled onto a way to slow the spread of the virus enough to manage it, but not before

nearly 60 million attacks had been conducted, Salim Neino, CEO of Kryptos Logic, testified June 15 at a joint hearing of two subcommittees of the House Science, Space & Technology Committee. Mr. Hutchins is employed by Kryptos Logic.

U.S. officials are keenly aware that a similar attack could happen here. In June, the federally sponsored Health Care Industry Cybersecurity Task Force issued a report on their year-long look at the state of the health care IT in this country. The task force was mandated by the Cybersecurity Act of 2015 and formed in March 2016.

“The health care system cannot deliver effective and safe care without deeper digital connectivity. If the health care system is connected, but insecure, this connectivity could betray patient safety, subjecting them to unnecessary risk,” according to the task force report. “Data collected for



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the good of patients and used to develop new treatments can be used for nefarious purposes such as fraud, identity theft, supply chain disruptions, the theft of research and development, and stock manipulation. Most importantly, cybersecurity attacks disrupt patient care.”

Specifically, the task force made the following recommendations:

- Define and streamline leadership, governance, and expectations for health care industry cybersecurity.
- Increase the security and resilience of medical devices and health IT.
- Develop the health care workforce capacity necessary to prioritize and ensure cybersecurity awareness and technical capabilities.
- Increase health care industry readiness through improved cybersecurity awareness and education.
- Identify mechanisms to protect research and development efforts and intellectual property from attacks or exposure.
- Improve information sharing of industry threats, weaknesses, and mitigations.

Health care cybercrime is a significant problem in the United States. In 2016, 328 U.S. health care firms reported data breaches, up from 268 in 2015, with a total of 16.6 million Americans affected, according to a report conducted by Bitglass, a security software company. In February 2016, a hospital in California was forced to pay about \$17,000 in Bitcoin, an electronic currency that is known to be favored by cybercriminals, to access electronic health records that were held in a similar manner to last month's attack on the NHS.

For physicians, this may seem like

someone else's problem; however, unsafe day-to-day interactions with connected devices and patient EHRs were among the task force's primary concerns.

For many, creating a safe password or not giving out critical information may seem like common sense, but many physicians are not able or willing to take the time to make sure they are interacting with systems safely, or they are overconfident in their security system, according to task force member Mark Jarrett, MD, senior vice president and chief quality officer at Northwell Health in New York.

“Most physicians now will try to access medical records of their patients who have been in the hospital because that's good care,” Dr. Jarrett said in an interview.

But they have to recognize that “they cannot give these passwords to other people and they need to make these passwords complex,” noted Dr. Jarrett.

“Phishing” is another concern. In a phishing scam, cybercriminals will pose as a fraudulent institution or individual in order to trick a target into downloading a virus, sending additional valuable information, or even paying money directly to the criminals.

“Physicians checking their emails need to be aware of possible phishing episodes, because they could be infected, and then there is the possibility that infection could be introduced into the system,” Dr. Jarrett said.

“I think the disconnect is [that physicians] are not used to [cybersecurity]. It's not part of their daily life and they also, up until recently, thought ‘it's never going to happen to me.’”

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VIEW ON THE NEWS

WannaCry provides wake-up call

When computer hackers took control of the United Kingdom's National Health Service using a virus known as WannaCry, doctors and nurses were left helpless, blocked from the files they would need to treat their patients until they paid to get those files back.

Doctors were forced to revert to older methods, slowing everything to a snail's pace.

The media coverage of the event was dramatic, but there is no doubt the effects made it justifiably so.

NHS hospitals had not achieved their goal of being paperless; had they been, the service would have been completely unable to stop the attack. It was not just software that was affected but medical devices as well. Physicians were unable to perform x-rays, and some hospitals found that the refrigerators used to store blood products were shut down.

While the NHS was particularly vulnerable to the WannaCry because of budget cuts, this cybercrime could have happened to any hospital, and its lessons are applicable for all.

Doctors do understand the value of patients records, but they seem to be unaware of the physical harm that could befall patients from a cyberattack.

This attack needs to serve as a wake-up call for health care professionals who are not invested in their facilities' cybersecurity practices.

Underfunding left NHS hospitals terribly exposed and, if physicians continue to be complacent with how to handle this issue, the results are sure to be more severe.

Rachel Clarke, MD, is at Oxford (England) University Hospitals NHS Foundation Trust, and Taryn Youngstein, MD, is at Imperial College Healthcare NHS Trust, London. They reported having no relevant financial conflicts of interest. Their remarks were made in a perspective published in the New England Journal of Medicine (doi: 10.1056/NEJMp1706754).



Take a different path

*INDICATIONS

- Adempas (riociguat) tablets is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.[†]

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

[†] Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.
- Patients with Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.



Adempas—the first and only approved treatment for both PAH (WHO Group 1) and CTEPH (WHO Group 4)* adult patients

Adempas has proven efficacy, as demonstrated by the following measures:

- Exercise capacity, as measured by 6MWD in PAH and CTEPH
- WHO Functional Class in PAH and CTEPH
- Hemodynamics: PVR and NT-proBNP in PAH and CTEPH
- Delayed time to clinical worsening in PAH†

Learn more or contact a representative at adempas-us.com



FOR PAH. FOR CTEPH.
Adempas[®]
riociguat tablets
0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

WARNINGS AND PRECAUTIONS (continued)

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

WARNINGS AND PRECAUTIONS (continued)

Pulmonary Veno-Occlusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions occurring more frequently ($\geq 3\%$) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%). Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the brief summary of the full Prescribing Information, including Boxed Warning, on the following pages.



Bayer
100 Bayer Boulevard, Whippany, NJ 07981 USA
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ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer Adempas to a pregnant female because it may cause fetal harm [see Contraindications (4.1), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception [see Dosage and Administration (2.3), Warnings and Precautions (5.1, 5.2), and Use in Specific Populations (8.6)].**
- **For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program [see Warnings and Precautions (5.1, 5.2)].**

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

4 CONTRAINDICATIONS

4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Dosage and Administration (2.6), Drug Interactions (7.1) and Clinical Pharmacology (12.2)]. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil.

4.4 Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (PH-IIP)

Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program [see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)].

5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program [see Warnings and Precautions (5.1)].

Important requirements of the Adempas REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.3)]
- Bleeding [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years [see Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo ($\geq 3\%$) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently ($\geq 3\%$) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension. Do not administer within 24 hours of sildenafil. Do not administer 24 hours before or within 48 hours after tadalafil [see Dosage and Administration (2.6)]. Clinical experience with co-administration of Adempas and other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50% to 60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see *Dosage and Administration (2.5)*, *Warnings and Precautions (5.3)* and *Clinical Pharmacology (12.3)*].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see *Clinical Pharmacology (12.3)*].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see *Boxed Warning and Contraindications (4.1)*].

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see *Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see *Clinical Studies (14)*]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see *Clinical Pharmacology (12.3)*].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see *Boxed Warning, Dosage and Administration (2.3)* and *Use in Specific Populations (8.1)*].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see *Clinical Pharmacology (12.3)*].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*]. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see *Warnings and Precautions (5.2)*]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.6)*].
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Instruct patients to report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see *Adverse Reactions (6.1)*]. Advise patients to be aware of how they react to Adempas before driving or operating machinery, and if needed, consult their physician. Patients should consult their physicians if dizziness gets worse with Adempas.

Manufactured for:



Bayer HealthCare

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New data update guidance on nonstatin LDL lowering

BY SHARON WORCESTER

Frontline Medical News

The American College of Cardiology Task Force on Expert Consensus Decision Pathways has released a “focused update” for the 2016 ACC Expert Consensus Decision Pathway (ECDP) on the role of nonstatin therapies for LDL cholesterol lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk.

The update was deemed by the ECDP writing committee to be desirable given the additional ev-

• Consideration of new randomized clinical trial data for the PCSK9 inhibitors evolocumab and bococizumab. Namely, they included results from the cardiovascular outcomes trials FOURIER (Fur-

ther Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and SPIRE-1 and SPIRE-2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events), which

were published in early 2017. • An adjustment in the ECDP algorithms with respect to thresholds for consideration of net ASCVD risk reduction. The 2016 ECDP thresholds for risk-reduction



‘This ECDP addresses current gaps in care for LDL-C lowering to reduce ASCVD risk.’

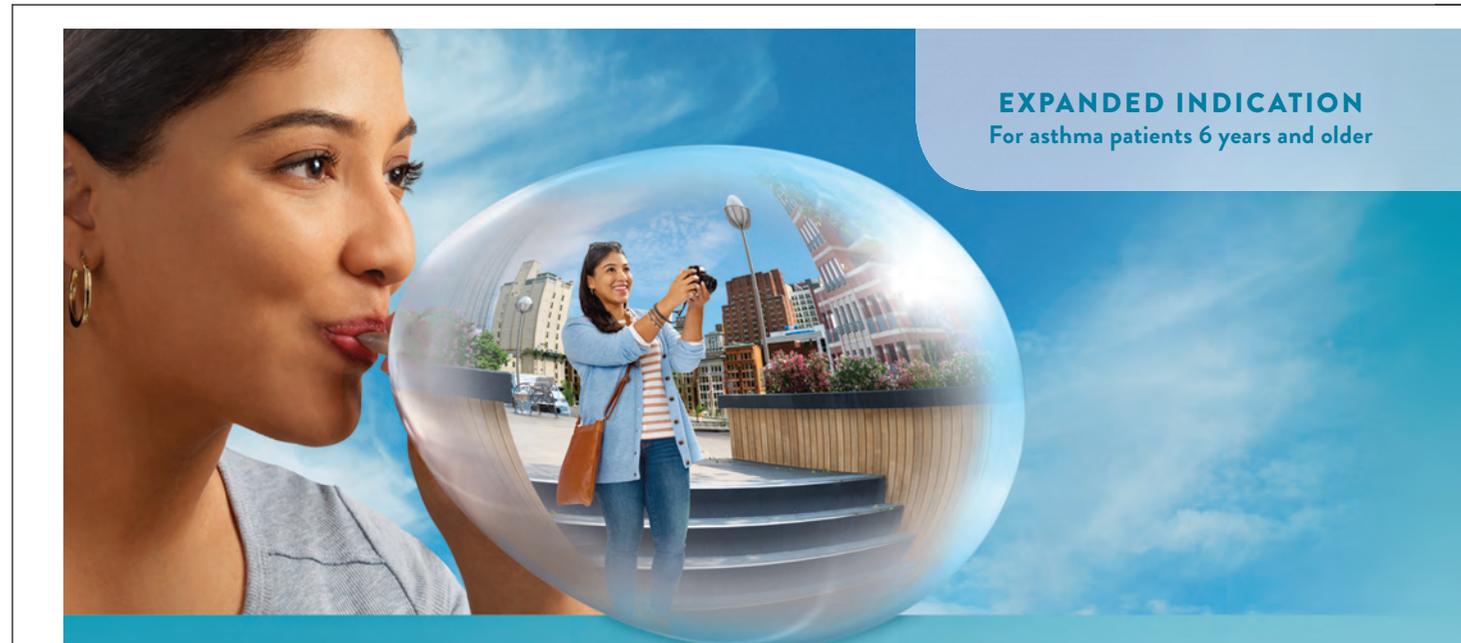
DR. LLOYD-JONES

idence and perspectives that have emerged since the publication of the 2016 version, particularly with respect to the efficacy and safety of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors for the secondary prevention of ASCVD, as well as the best use of ezetimibe in addition to statin therapy after acute coronary syndrome.

“This ECDP addresses current gaps in care for LDL-C lowering to reduce ASCVD risk and provides recommendations that build on the evidence base established by the 2013 [American College of Cardiology/American Heart Association] cholesterol guideline,” explained the committee, which was chaired by Donald M. Lloyd-Jones, MD, of Northwestern University, Chicago (J Am Coll Cardiol. 2017. doi: 10.1016/j.jacc.2017.07.745)

The ECDP algorithms endorse the four evidence-based statin benefit groups identified in the 2013 guidelines (adults aged 21 and older with clinical ASCVD, adults aged 21 and older with LDL-C of 190 mg/dL or greater, adults aged 40-75 years without ASCVD but with diabetes and with LDL-C of 70-189 mg/dL, and adults aged 40-75 without ASCVD or diabetes but with LDL-C of 70-189 mg/dL and an estimated 10-year risk for ASCVD of 7.5% or greater) and assume that the patient is currently taking or has attempted to take a statin, they noted.

Among the changes in the 2017 focused update are:



EXPANDED INDICATION
For asthma patients 6 years and older

For uncontrolled asthma in patients aged ≥ 6 years on ICS or ICS + LABA

SPIRIVA RESPIMAT—A different approach adds new expectations for asthma

SPIRIVA RESPIMAT, 1.25 mcg, is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 6 years of age and older. SPIRIVA RESPIMAT is not indicated for relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

SPIRIVA RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any component of this product. Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an attack, a rapid-acting beta₂-agonist should be used.

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, discontinue SPIRIVA RESPIMAT at once and consider alternative treatments. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT.

Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated with an inhaled short-acting beta₂-agonist, such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered.

SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.



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benefit were percent reduction in LDL-C with consideration of absolute LDL-C level in patients with clinical ASCVD, baseline LDL-C of 190 mg/dL or greater, and primary prevention. In patients with diabetes with or without clinical ASCVD, clinicians were allowed to consider absolute LDL-C and/or non-HDL-cholesterol levels. In the

2017 ECDP update, the thresholds are percent reduction in LDL-C with consideration of absolute LDL-C or non-HDL-C levels for patients in each of the four statin benefit groups. This change was based on the inclusion criteria of the FOURIER trial, the ongoing ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes

After an Acute Coronary Syndrome During Treatment With Alirocumab), and the SPIRE-2 trial, all of which included non-HDL-C thresholds. "In alignment with these inclusion criteria, the 2017 Focused Update includes both LDL-C and non-HDL-C thresholds for evaluation of net ASCVD risk-reduction benefit

when considering the addition of nonstatin therapies for patients in each of the four statin benefit groups" the update explained.

- An expansion of the threshold for consideration of net ASCVD risk-reduction benefit from a reduction of LDL C of at least 50%, as well as consideration of LDL-C

Continued on following page

SPIRIVA RESPIMAT is an add-on maintenance treatment for asthma with proven efficacy and a demonstrated safety profile for patients aged ≥ 6 years



Works differently to address bronchoconstriction



Improves lung function* in asthma patients on ICS or ICS + LABA



Reduces the risk and rate of exacerbations in adult patients†

*For peak forced expiratory volume in 1 second ($FEV_{1,0-3hr}$) and trough FEV_1 .

†In clinical trials, an asthma exacerbation was defined as an episode of progressive increase in ≥ 1 asthma symptom(s) (like shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms) or a decrease of a patient's best morning peak expiratory flow (PEF) of 30% from a patient's mean morning PEF for ≥ 2 consecutive days that required the initiation or increase in treatment with systemic steroids for ≥ 3 days.

ICS, inhaled corticosteroids; LABA, long-acting beta₂-agonist.

SPIRIVA RESPIMAT for ASTHMA | 1.25 mcg/puff

Visit AddOnForAsthma.com to learn more



IMPORTANT SAFETY INFORMATION (continued)

Since dizziness and blurred vision may occur with the use of SPIRIVA RESPIMAT, caution patients about engaging in activities such as driving a vehicle, or operating appliances or machinery.

SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment (creatinine clearance of < 60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

The most common adverse reactions $> 2\%$ incidence and higher than placebo with SPIRIVA RESPIMAT (placebo) in asthma trials in adults were pharyngitis 15.9% (12.4%), headache 3.8% (2.7%), bronchitis 3.3% (1.4%), and sinusitis 2.7% (1.4%). The adverse reaction profile for adolescent and pediatric patients was comparable to that observed in adult patients with asthma.

SPIRIVA RESPIMAT may interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs.

Inform patients not to spray SPIRIVA RESPIMAT into the eyes as this may cause blurring of vision and pupil dilation.

Please see Brief Summary of full Prescribing Information on the following pages.

Reference: SPIRIVA RESPIMAT [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2017.



less than 70 mg/dL or non-HDL-C less than 100 mg/dL for all patients (that is, both those with and those without comorbidities) who have clinical ASCVD and baseline LDL-C of 70-189 mg/dL. The 2016 ECDP had different thresholds for those with versus those without comorbidities. This change was

based on findings from the FOURIER trial and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). “Based on consideration of all available evidence, the consensus of the writing committee members is that lower LDL-C levels are safe and optimal in patients with clinical ASCVD due to [their] in-

creased risk of recurrent events,” they said.

- An expanded recommendation on the use of ezetimibe and PCSK9 inhibition. The 2016 ECDP stated that, “if a decision is made to proceed with the addition of nonstatin therapy to maximally tolerated statin therapy, it is reasonable to consider the

addition of ezetimibe as the initial agent and a PCSK9 inhibitor as the second agent.” However, based on the FOURIER findings, the ongoing ODYSSEY Outcomes trial, and IMPROVE-IT, the 2017 Focused Update states that, if such a decision is made in patients with clinical ASCVD with comorbidities and baseline

SPIRIVA® Respimat® (tiotropium bromide) inhalation spray Rx only
FOR ORAL INHALATION

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE: Maintenance Treatment of Chronic Obstructive Pulmonary Disease: SPIRIVA RESPIMAT (tiotropium bromide) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA RESPIMAT is indicated to reduce exacerbations in COPD patients. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm. **Maintenance Treatment of Asthma:** SPIRIVA RESPIMAT is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 6 years of age and older. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS: SPIRIVA RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any component of this product [see *Warnings and Precautions*]. In clinical trials with SPIRIVA RESPIMAT, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported [see *Warnings and Precautions*].

WARNINGS AND PRECAUTIONS: Not for Acute Use: SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for COPD and asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an acute attack, a rapid-acting beta₂-agonist should be used. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, therapy with SPIRIVA RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT. **Paradoxical Bronchospasm:** Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta₂-agonist such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered. **Worsening of Narrow-Angle Glaucoma:** SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

ADVERSE REACTIONS: The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see *Warnings and Precautions*]; Paradoxical bronchospasm [see *Warnings and Precautions*]; Worsening of narrow-angle glaucoma [see *Warnings and Precautions*]; Worsening of urinary retention [see *Warnings and Precautions*]. Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared

to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. Since the same active ingredient (tiotropium bromide) is administered to COPD and asthma patients, prescribers and patients should take into account that the observed adverse reactions could be relevant for both patient populations independent of dosage strength. **Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:** The SPIRIVA RESPIMAT clinical development program included ten placebo controlled clinical trials in COPD. Two trials were four-week cross-over trials and eight were parallel group trials. The parallel group trials included a three week dose-ranging trial, two 12-week trials, three 48-week trials, and two trials of 4-week and 24 week duration conducted for a different program that contained tiotropium bromide 5 mcg treatment arms. The primary safety database consists of pooled data from the 7 randomized, parallel-group, double-blind, placebo-controlled studies of 4-48 weeks in treatment duration. These trials included 6565 adult COPD patients (75% males and 25% females) 40 years of age and older. Of these patients, 3282 patients were treated with SPIRIVA RESPIMAT 5 mcg and 3283 received placebo. The SPIRIVA RESPIMAT 5 mcg group was composed mostly of Caucasians (78%) with a mean age of 65 years and a mean baseline percent predicted post-bronchodilator FEV₁ of 46%. In these 7 clinical trials, 68.3% of patients exposed to SPIRIVA RESPIMAT 5 mcg reported an adverse event compared to 68.7% of patients in the placebo group. There were 68 deaths in the SPIRIVA RESPIMAT 5 mcg treatment group (2.1%) and 52 deaths (1.6%) in patients who received placebo. The percentage of SPIRIVA RESPIMAT patients who discontinued due to an adverse event were 7.3% compared to 10% with placebo patients. The percentage of SPIRIVA RESPIMAT 5 mcg patients who experienced a serious adverse event were 15.0% compared to 15.1% with placebo patients. In both groups, the adverse event most commonly leading to discontinuation was COPD exacerbation (SPIRIVA RESPIMAT 2.0%, placebo 4.0%) which was also the most frequent serious adverse event. The most commonly reported adverse reactions were pharyngitis, cough, dry mouth, and sinusitis (Table 1). Other adverse reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, dysuria, and urinary retention. Table 1 shows all adverse reactions that occurred with an incidence of >3% in the SPIRIVA RESPIMAT 5 mcg treatment group, and a higher incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo.

Table 1 Number (Percentage) of COPD Patients Exposed to SPIRIVA RESPIMAT 5 mcg with Adverse Reactions >3% (and Higher than Placebo): Pooled Data from 7 Clinical Trials with Treatment Periods Ranging between 4 and 48 Weeks in COPD Patients

Body System (Reaction)*	SPIRIVA RESPIMAT 5 mcg [n=3282]	Placebo [n=3283]
Gastrointestinal Disorders		
Dry mouth	134 (4.1)	52 (1.6)
Infections and Infestations		
Pharyngitis	378 (11.5)	333 (10.1)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	190 (5.8)	182 (5.5)
Sinusitis	103 (3.1)	88 (2.7)

*Adverse reactions include a grouping of similar terms. Other reactions that occurred in the SPIRIVA RESPIMAT 5 mcg group at an incidence of 1% to 3% and at a higher incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo included: *Cardiac disorders:* palpitations; *Gastrointestinal disorders:* constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders:* dizziness; *Respiratory, thoracic, and mediastinal disorders:* dysphonia; *Skin and subcutaneous tissue disorders:* pruritus, rash; *Renal and urinary disorders:* urinary tract infection. *Less Common Adverse Reactions:* Among the adverse reactions observed in the

clinical trials with an incidence of <1% and at a higher incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo were: dysphagia, gingivitis, intestinal obstruction including ileus paralytic, joint swelling, dysuria, urinary retention, epistaxis, laryngitis, angioedema, dry skin, skin infection, and skin ulcer. **Clinical Trials Experience in Asthma: Adult Patients:** SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in four placebo-controlled parallel-group trials ranging from 12 to 52 weeks of treatment duration in adult patients (aged 18 to 75 years) with asthma. The safety data described below are based on one 1-year, two 6-month and one 12-week randomized, double-blind, placebo-controlled trials in a total of 2849 asthma patients on background treatment of at least ICS or ICS and long-acting beta agonist (ICS/LABA). Of these patients, 787 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 59.7% were female and 47.5% were Caucasian with a mean age of 43.7 years and a mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV₁) of 90.0% at baseline. Table 2 shows all adverse reactions that occurred with an incidence of >2% in the SPIRIVA RESPIMAT 2.5 mcg treatment group, and a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo.

Table 2 Number (Percentage) of Asthma Patients Exposed to SPIRIVA RESPIMAT 2.5 mcg with Adverse Reactions >2% (and Higher than Placebo): Pooled Data from 4 Adult Clinical Trials with Treatment Periods Ranging between 12 and 52 Weeks in Asthma Patients

Body System (Reaction)*	SPIRIVA RESPIMAT 2.5 mcg [n=787]	Placebo [n=735]
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngitis	125 (15.9)	91 (12.4)
Sinusitis	21 (2.7)	10 (1.4)
Bronchitis	26 (3.3)	10 (1.4)
Nervous System Disorders		
Headache	30 (3.8)	20 (2.7)

*Adverse reactions include a grouping of similar terms. Other reactions that occurred in the SPIRIVA RESPIMAT 2.5 mcg group at an incidence of 1% to 2% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo included: *Nervous system disorders:* dizziness; *Gastrointestinal disorders:* oropharyngeal, candidiasis, diarrhea; *Respiratory, thoracic, and mediastinal disorders:* cough, rhinitis allergic; *Renal and urinary disorders:* urinary tract infection; *General disorders and administration site conditions:* pyrexia; and *Vascular disorders:* hypertension. *Less Common Adverse Reactions:* Among the adverse reactions observed in the clinical trials with an incidence of 0.5% to <1% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo were: palpitations, dysphonia, acute tonsillitis, tonsillitis, rhinitis, herpes zoster, gastroesophageal reflux disease, oropharyngeal discomfort, abdominal pain upper, insomnia, hypersensitivity (including immediate reactions), angioedema, dehydration, arthralgia, muscle spasms, pain in extremity, chest pain, hepatic function abnormal, liver function test abnormal. *Adolescent Patients Aged 12 to 17 years:* SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in adolescent patients with asthma. The safety data described below are based on one 48-week and one 12-week double-blind, placebo-controlled trials in a total of 789 adolescent asthma patients on background treatment of at least ICS or ICS plus one or more controller. Of these patients, 252 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 63.9% were male and 95.6% were Caucasian with a mean age of 14.3 years and a mean post-bronchodilator percent predicted FEV₁ of 98.3% at baseline. The adverse reaction profile for adolescent patients with asthma was comparable to that observed in adult patients with asthma. *Pediatric Patients Aged 6 to 11 years:* SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in two placebo-controlled parallel-group trials ranging from 12 to

LDL-C of 70-189 mg/dL, it is reasonable to weigh the addition of either ezetimibe or a PCSK9 inhibitor in light of “considerations of the additional percent LDL-C reduction desired, patient preferences, costs, route of administration, and other factors.” The update also spells out considerations that may favor the

initial choice of ezetimibe versus a PCSK9 inhibitor (such as requiring less than 25% additional lowering of LDL-C, an age of over 75 years, cost, and other patient factors and preferences).
 • Additional factors, based on the FOURIER trial results and inclusion criteria, that may be considered for the identification

of higher-risk patients with clinical ASCVD. The 2016 ECDP included on this list diabetes, a recent ASCVD event, an ASCVD event while already taking a statin, poorly controlled other major ASCVD risk factors, elevated lipoprotein, chronic kidney disease, symptomatic heart failure, maintenance hemodialysis, and

baseline LDL-C of at least 190 mg/dL not due to secondary causes. The 2017 update added being 65 years or older, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic peripheral artery disease with prior MI or stroke, history of non-MI related coronary revascularization, residual coronary artery disease with at least 40% stenosis in at least two large vessels, HDL-C less than 40 mg/dL for men and less than 50 mg/dL for women, high-sensitivity C-reactive protein greater than 2 mg/L, and metabolic syndrome.

The content of the full ECDP has been changed in accordance with

‘The 2017 Focused Update includes both LDL-C and non-HDL-C thresholds for evaluation of net ASCVD risk-reduction benefit when considering the addition of nonstatin therapies for patients in each of the four statin benefit groups.’

these updates and now includes more extensive and detailed guidance for decision making – both in the text and in treatment algorithms.

Aspects that remain unchanged include the decision pathways and algorithms for the use of ezetimibe or PCSK9 inhibitors in primary prevention patients with LDL-C less than 190 mg/dL or in those without ASCVD and LDL-C of 190 mg/dL or greater unattributable to secondary causes.

In addition to other changes made for the purpose of clarification and consistency, recommendations regarding bile acid-sequestrant use were downgraded; these are now only recommended as optional secondary agents for consideration in patients who cannot tolerate ezetimibe.

“[These] recommendations attempt to provide practical guidance for clinicians and patients regarding the use of nonstatin therapies to further reduce ASCVD risk in situations not covered by the guideline until such time as the scientific evidence base expands and cardiovascular outcomes trials are completed with new agents for ASCVD risk reduction,” the committee concluded.

Dr. Lloyd-Jones reported having no disclosures.

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48 weeks of treatment duration in pediatric patients aged 6 to 11 years with asthma. The safety data are based on one 48-week and one 12-week double-blind, placebo-controlled trials in a total of 801 pediatric asthma patients aged 6 to 11 years on background treatment of at least ICS or ICS plus one or more controller. Of these patients, 271 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 71.2% were male and 86.7% were Caucasian with a mean age of 8.9 years and a mean post-bronchodilator percent predicted FEV₁ of 97.9% at baseline. The adverse reaction profile for pediatric patients aged 6 to 11 years with asthma was comparable to that observed in adult patients with asthma. SPIRIVA RESPIMAT 5 mcg also has been compared to placebo in seven placebo-controlled parallel-group trials ranging from 12 to 52 weeks of treatment duration in 4149 adult patients (aged 18 to 75 years) with asthma and in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in 789 adolescent patients (1370 adults and 264 adolescents receiving SPIRIVA RESPIMAT 5 mcg once-daily). The adverse reaction profile for SPIRIVA RESPIMAT 5 mcg in patients with asthma was comparable to that observed with SPIRIVA RESPIMAT 2.5 mcg in patients with asthma. **Postmarketing Experience:** In addition to the adverse reactions observed during the SPIRIVA RESPIMAT clinical trials in COPD, the following adverse reactions have been observed during post-approval use of SPIRIVA RESPIMAT 5 mcg and another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Glaucoma, intraocular pressure increased, vision blurred; Atrial fibrillation, tachycardia, supraventricular tachycardia; Bronchospasm; Glossitis, stomatitis; Dehydration; Insomnia; Hypersensitivity (including immediate reactions), and urticaria.

DRUG INTERACTIONS: Concomitant Respiratory Medications: SPIRIVA RESPIMAT has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, and anti-IgE treatment without increases in adverse reactions. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions and Adverse Reactions].

USE IN SPECIFIC POPULATIONS: Pregnancy: **Risk Summary:** The limited human data with SPIRIVA RESPIMAT use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. There are risks to the mother and the fetus associated with poorly controlled asthma in pregnancy [see Clinical Considerations]. Based on ani-

mal reproduction studies, no structural abnormalities were observed when tiotropium was administered by inhalation to pregnant rats and rabbits during the period of organogenesis at doses 790 and 8 times, respectively, the maximum recommended human daily inhalation dose (MRHDID). Increased post-implantation loss was observed in rats and rabbits administered tiotropium at maternally toxic doses 430 times and 40 times the MRHDID, respectively [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **Clinical Considerations: Disease-Associated Maternal and/or Embryo-Fetal Risk:** Poorly or moderately controlled asthma in pregnancy increases the maternal risk of preeclampsia and infant prematurity, low birth weight, and small for gestational age. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control. **Data: Animal Data:** In 2 separate embryo-fetal development studies, pregnant rats and rabbits received tiotropium during the period of organogenesis at doses up to approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m² basis at inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at tiotropium doses of approximately 40 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at a tiotropium dose of approximately 430 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m² basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). **Lactation: Risk Summary:** There are no data on the presence of tiotropium in human milk, the effects on the breastfed infant, or the effects on milk production. Tiotropium is present in milk of lactating rats; however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPIRIVA RESPIMAT and any potential adverse effects on the breastfed child from SPIRIVA RESPIMAT or from the underlying maternal condition. **Data:** The distribution of tiotropium bromide into milk was investigated after a single intravenous administration of 10 mg/kg to lactating rats. Tiotropium and/or its metabolites are present in the milk of lactating rats at concentrations above those in plasma. **Pediatric Use:** The safety and efficacy of SPIRIVA RESPIMAT 2.5 mcg have been established in pediatric patients aged 6 to

17 years with asthma in 6 clinical trials up to 1 year in duration. In three clinical trials, 327 patients aged 12 to 17 years with asthma were treated with SPIRIVA RESPIMAT 2.5 mcg; in three additional clinical trials, 345 patients aged 6 to 11 years with asthma were treated with SPIRIVA RESPIMAT 2.5 mcg. Patients in these age groups demonstrated efficacy results similar to those observed in patients aged 18 years and older with asthma. The safety and efficacy of SPIRIVA RESPIMAT have not been established in pediatric patients less than 6 years of age. The safety of SPIRIVA RESPIMAT 2.5 mcg has been studied in pediatric patients with asthma aged 1 to 5 years who were on background treatment of at least ICS in one placebo-controlled clinical trial of 12 weeks duration (36 treated with SPIRIVA RESPIMAT 2.5 mcg and 34 with placebo RESPIMAT). In this study, SPIRIVA RESPIMAT or placebo RESPIMAT was delivered with the AeroChamber Plus Flow-Vu® valved holding chamber with facemask once daily. The majority of the patients in the trial were male (60.4%) and Caucasian (76.2%) with a mean age of 3.1 years. The adverse reaction profile was similar to that observed in adults and older pediatric patients [See Adverse Reactions]. **In Vitro Characterization Studies with Valved Holding Chamber:** Dose delivery and fine particle fraction of SPIRIVA RESPIMAT when administered via a valved holding chamber (Aero-Chamber Plus Flow-Vu® with or without face mask) was assessed by *in vitro* studies. Inspiratory flow rates of 4.9, 8.0, and 12.0 L/min in combination with holding times of 0, 2, 5, and 10 seconds were tested. The flow rates were selected to be representative of inspiratory flow rates of children aged 6 to 12 months, 2 to 5 years, and over 5 years, respectively. Table 3 summarizes the results for delivered dose under the respective test conditions and configurations. The *in vitro* study data show a reduction of the absolute delivered dose through the valved holding chamber. However, in terms of dose per kilogram of body weight the data suggest that under all tested conditions the dose of SPIRIVA RESPIMAT delivered by the Aero-Chamber Plus Flow-Vu® valved holding chamber with mask will at least lead to a dosing comparable to that of adults without use of a holding chamber and mask (Table 3). The fine particle fraction (< 5 µm) across the flow rates used in these studies was 69-89% of the delivered dose through the valved holding chamber, consistent with the removal of the coarser fraction by the holding chamber. In contrast, the fine particle fraction for SPIRIVA RESPIMAT delivered without a holding chamber typically represents approximately 60% of the delivered dose. **Geriatric Use:** Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted. Thirty nine percent of SPIRIVA RESPIMAT clinical trial patients with COPD were between 65 and 75 years of age and 14% were greater than or equal to 75 years of age. Approximately seven percent of SPIRIVA RESPIMAT clinical trial patients with asthma were greater than or equal to 65 years of age. The adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Renal Impairment:** Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [see Warnings and Precautions]. **Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. **OVERDOSAGE:** High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. Treatment of overdose consists of discontinuation of SPIRIVA RESPIMAT together with institution of appropriate symptomatic and/or supportive therapy.

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Table 3 In Vitro Medication Delivery through AeroChamber Plus Flow-Vu® Valved Holding Chamber with Face Mask at Different low Rates and Holding Times Using the Dose 2.5 mcg (as two actuations)

Flow Rate (L/min) and corresponding age	Mask	Holding Time (seconds)	Mean Medication Delivery through AeroChamber Plus Flow-Vu® per Dose (mcg)	Body Weight 50 th Percentile (kg) ^a	Medication Delivered per Dose (ng/kg) ^b
4.9 (6 to 12 Months)	small	0	0.85	7.5-9.9	86-113
		2	0.86		87-115
		5	0.55		56-73
		10	0.62		63-83
8.0 (2 to 5 Years)	medium	0	0.74	12.3-18.0	41-60
		2	0.93		52-76
		5	0.72		40-59
		10	0.57		32-46
12.0 (> 5 Years)	medium	0	1.16	18.0	64
		2	0.96		53
		5	0.78		43
		10	0.61		34

^aCenters for Disease Control growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2009).

^bBody weight values correspond to the average of the 50 percentile weight for boys and girls at the ages indicated.

^cInhalation of SPIRIVA RESPIMAT 2.5 mcg dose (as two actuations) in a 70-kg adult without use of a valved holding chamber and mask delivers approximately 2.5 mcg, or 36 ng/kg.

Rivaroxaban plus aspirin cut cardiovascular events in stable patients

BY MITCHEL L. ZOLER

Frontline Medical News

BARCELONA – Combined treatment with a very low dosage of the anti-coagulant rivaroxaban plus low-dose aspirin produced significant cuts in major adverse coronary, cerebral, and peripheral artery disease events with just a modest rise in major bleeding events in patients with stable disease in the COMPASS pivotal, randomized trial with more than 27,000 patients.

The benefits from the rivaroxaban plus aspirin regimen included a statistically significant 24% relative risk reduction in the study's primary, combined endpoint, and a significant 18% relative risk reduction in all-cause death, compared with a standard regimen of aspirin only, John W. Eikelboom, MD, said at the annual congress of the European Society of Cardiology. In addition, analysis of the net clinical benefit from treatment that took into account both the major adverse cardiovascular events prevented and major bleeding events induced, showed that the rivaroxaban-plus-aspirin regimen cut these

by a statistically significant 20%, compared with aspirin alone.

Other notable benefits documented by the findings included a statistically significant 42% relative risk reduction for stroke and a statistically significant 46% relative risk reduction in the incidence of major adverse limb events among the roughly one-quarter of enrolled patients who entered the study with evidence of peripheral artery disease.

These risk reductions are similar in magnitude to the secondary-prevention benefits produced by controlling hypertension or dyslipidemia, noted Dr. Eikelboom, a researcher at McMaster University in Hamilton, Ont. "In the future, rivaroxaban will take its place among the other foundational treatments for long-term, secondary prevention," he predicted in a video interview, available on CHEST Physician's web site at <http://www.mdedge.com/chestphysician/article/145492/cad-atherosclerosis/video-rivaroxaban-plus-aspirin-cut-cardiovascular>.

The COMPASS trial produced "unambiguous results that should change guidelines and the management of stable coronary artery



Mitchel L. Zoler/Frontline Medical News

Dr. John W. Eikelboom

disease," commented Eugene Braunwald, MD, designated discussant for Dr. Eikelboom's report. The results are "an important step for thrombocardiology," said Dr. Braunwald, professor of medicine at Harvard Medical School in Boston.

Concurrently with Dr. Eikelboom's report the results appeared in an article published online (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMoa1709118). This publication also include an editorial by Dr. Braunwald (N Engl J Med. 2017 Aug 27. doi: 10.1056/NEJMe1710241).

The Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial enrolled 27,395 patients with stable coronary,

'In the future, rivaroxaban will take its place among the other foundational treatments for long-term, secondary prevention.'

carotid, or peripheral artery disease, or a combination of two or more of these, at 602 centers in 33 countries. About 90% of enrolled patients had coronary artery disease and 27% had peripheral artery disease. The enrolled patients averaged 68 year old and were an average of 7 years removed from their index arterial event. Randomization assigned patients to receive 2.5 mg rivaroxaban (Xarelto) twice daily plus 100 mg aspirin daily, 5 mg rivaroxaban twice daily, or 100 mg aspirin once daily. The trial stopped early, after an average follow-up of 23 months, because of the overwhelming benefit seen for the rivaroxaban plus aspirin combination. The rivarox-

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VIEW ON THE NEWS

Low-dose rivaroxaban benefits despite increased bleeding

The key message from COMPASS was that, although adding a very low dosage of rivaroxaban to aspirin in patients with stable coronary or peripheral artery disease resulted in a clear increase in major bleeding events, patients received an overall net beneficial effect from the combined regimen. The finding that clinches the net benefit from the rivaroxaban plus aspirin combination, compared with aspirin alone, was that the combined regimen produced a statistically significant relative risk reduction of 18% for all-cause mortality. This finding reinforces the idea that the primary outcome was beneficial despite an increase in major bleeding events.

The finding that rivaroxaban plus aspirin produced benefit with a modest increase in bleeding risk in patients with peripheral artery disease (PAD) is especially important because PAD is really difficult to treat. Very few interventions have previously been proven to have a beneficial effect for patients with PAD. It's very important to find

an intervention that can reduce critical limb ischemia events in addition to reducing coronary events, stroke, and overall mortality.

The very low dosage of rivaroxaban used in COMPASS, 2.5 mg twice daily, seems to be a very important part of the study's design. This dosage appeared to hit the sweet spot of being large enough to reduce events but with a gentle enough anticoagulation effect to avoid a significant increase in fatal, intracerebral, or critical organ bleeds. However, the patients enrolled in COMPASS, like most patients who enter trials, were generally at a lower risk for bleeding complications than we usually see in routine practice in patients with stable coronary or peripheral artery disease. Presuming that the Food and Drug Administration will soon approve the 2.5-mg formulation of rivaroxaban used in COMPASS, clinicians will need to be careful using this regimen on patients at increased risk for bleeding, such as frail or elderly patients with a history of bleeding events or taking other treatments that could increase bleeding risk, such as nonsteroidal anti-inflammatory drugs. In general, clinicians are wary of using treatments that in-

crease bleeding risk, and so they may hesitate to use this combination of rivaroxaban plus aspirin in patients with a high bleeding risk.

The success of the approach used in COMPASS became possible with the introduction of the new oral anticoagulant drugs. Now that this class of agents has been available for a few years, clinicians have grown increasingly comfortable with them, compared with warfarin. When the new oral anticoagulants first came out, many considered them similar to warfarin. Today, there is a better appreciation that these drugs are distinct from warfarin by really causing fewer bleeding complications.

Christopher B. Granger, MD, is a cardiologist and professor of medicine at Duke University in Durham, N.C. He has been a consultant to and has received research support from Bayer and from other drugs companies that market new oral anticoagulants. He made these comments in an interview.



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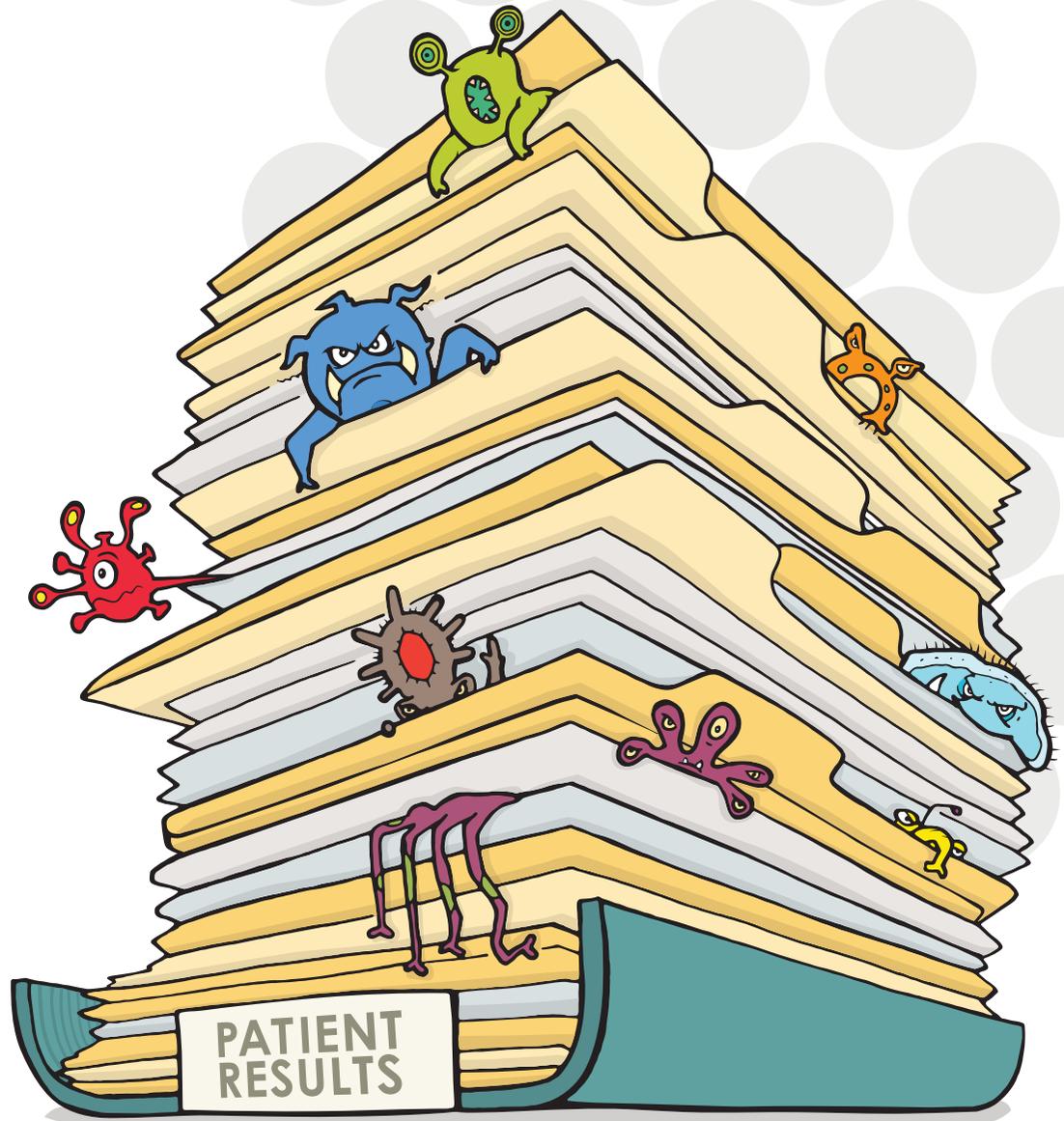
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aban-monotherapy arm failed to show any statistically significant benefits, compared with the aspirin-monotherapy control group.

The study's primary endpoint – the combined rate of cardiovascular disease death, nonfatal stroke, and nonfatal MI – occurred in 4.1% of patients in the rivaroxaban-plus-aspirin group and in 5.4% of patients on aspirin alone. The rate of major bleeding events was 3.1% among patients on rivaroxaban plus aspirin and 1.9% in those who received aspirin only, a 51% relative increase among patients on the dual regimen, but the results showed no statistically significant increase in the rates of fatal bleeds, intracerebral bleeds, or bleeding in other critical organs.

Sonia Anand, MD, a colleague of Dr. Eikelboom's at McMaster, presented a separate set of analyses that focused on the 7,470 enrolled patients who had been diagnosed at enrollment with peripheral artery disease. In this subgroup, the rivaroxaban-plus-aspirin regimen produced a statistically significant 28% relative risk reduction in the rate of the primary endpoint, compared with the aspirin control group. The dual regimen also produced a statistically significant 46% relative risk reduction in major



Dr. Sonia Anand

adverse limb events and a significant 70% relative reduction in the incidence of major lower-extremity amputations, reported Dr. Anand, professor of medicine and director of the vascular medicine clinic at McMaster.

The COMPASS findings follow a 2012 published report from the ATLAS ACS 2-TIMI 51 trial showing that treatment with the same low-dose rivaroxaban regimen plus aspirin and a thienopyridine (clopidogrel or ticlopidine) reduced the same combined triple endpoint by a statistically significant 16%, compared with aspirin and a thienopyridine alone, in patients with a recent



Dr. Eugene Braunwald

acute coronary syndrome event (N Engl J Med. 2012 Jan 5;366[1]:9-19). Despite this evidence, the Food and Drug Administration never approved the 2.5-mg formulation of rivaroxaban, nor did it approve marketing of rivaroxaban for this acute coronary syndrome population. This decision may have been driven in part by a problem with incomplete follow-up of several of the enrolled patients.

The COMPASS results were “very consistent” with the ATLAS ACS 2-TIMI 51 results, noted Dr. Eikelboom. “I think it's time to look at these two trials in combination,” he suggested. Availability of the 2.5-mg

rivaroxaban formulation used in both trials would allow “a treatment strategy that could start early after an acute coronary syndrome event and then extend long term,” he said.

COMPASS was sponsored by Bayer, which markets rivaroxaban (Xarelto). Dr. Eikelboom has received research support from Bayer and also from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Janssen, Pfizer, Portola, and Sanofi. Dr. Anand has received speaking honoraria from several drug companies. Dr. Braunwald had no relevant financial disclosures.

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Idarucizumab reversed dabigatran completely, rapidly

BY AMY KARON

Frontline Medical News

One IV 5-g dose of idarucizumab completely, rapidly, and safely reversed the anticoagulant effect of dabigatran, according to final results for 503 patients in the multicenter, prospective, open-label, uncontrolled RE-VERSE AD study.

Uncontrolled bleeding stopped a median of 2.5 hours after 134 patients received idarucizumab. In a separate group of 202 patients, 197 were able to undergo urgent procedures after a median of 1.6 hours, Charles V. Pollack Jr., MD, and his associates reported at the International Society on Thrombosis and Haemostasis congress. The report was simultaneously published in the New England Journal of Medicine.

The study uncovered no serious safety signals, and rates of thrombosis were 4.8% and 6.8% at 30 and 90 days, respectively, which resembled other reports of these patient populations (N Engl J Med. 2017 Jul 11. doi: 10.1056/NEJMoa1707278).

Idarucizumab was specifically developed to reverse the anticoagulant effect of dabigatran. Many countries

have already licensed the humanized monoclonal antibody fragment based on interim results for the first 90 patients enrolled in the Reversal Effects of Idarucizumab on Active



Uncontrolled bleeding stopped a median of 2.5 hours after 134 patients received idarucizumab.

DR. POLLACK

Dabigatran (RE-VERSE AD) study (NCT02104947), noted Dr. Pollack, of Thomas Jefferson University, Philadelphia.

The final RE-VERSE AD cohort included 301 patients with uncontrolled gastrointestinal, intracranial, or trauma-related bleeding and 202 patients who needed urgent procedures. Participants from both groups typically were white, in their late 70s (age range, 21-96 years), and receiving 110 mg (75-150 mg) dabigatran twice daily. The primary endpoint was maximum percentage reversal within 4 hours after patients

received idarucizumab, based on diluted thrombin time and ecarin clotting time.

The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100%-100%) in more than 98% of patients, and the effect usually lasted 24 hours. Among patients who underwent procedures, intraprocedural hemostasis was considered normal in 93% of cases, mildly abnormal in 5% of cases, and moderately abnormal in 2% of cases, the researchers noted. Seven patients received another dose of idarucizumab after developing recurrent or postoperative bleeding.

A total of 24 patients had an adjudicated thrombotic event within 30 days after receiving idarucizumab. These events included pulmonary embolism, systemic embolism, ischemic stroke, deep vein thrombosis, and myocardial infarction. The fact that many patients did not restart anticoagulation could have contributed to these thrombotic events, the researchers asserted. They noted that idarucizumab had no procoagulant activity in studies of animals and healthy human volunteers.

About 19% of patients in both groups died within 90 days. “Patients enrolled in this study were elderly, had numerous coexisting conditions, and presented with serious index events, such as intracranial hemorrhage, multiple trauma, sepsis, acute abdomen, or open fracture,” the investigators wrote. “Most of the deaths that occurred within 5 days after enrollment appeared to be related to the severity of the index event or to coexisting conditions, such as respiratory failure or multiple organ failure, whereas deaths that occurred after 30 days were more likely to be independent events or related to coexisting conditions.”

Boehringer Ingelheim Pharmaceuticals provided funding. Dr. Pollack disclosed grant support from Boehringer Ingelheim during the course of the study and ties to Daiichi Sankyo, Portola, CSL Behring, Bristol-Myers Squibb/Pfizer, Janssen Pharma, and AstraZeneca. Eighteen coinvestigators also disclosed ties to Boehringer Ingelheim and a number of other pharmaceutical companies. Two coinvestigators had no relevant financial disclosures.

Bad news keeps piling up for Absorb coronary scaffold

BY BRUCE JANCIN

Frontline Medical News

PARIS – Device thrombosis occurred nearly four times more frequently in recipients of the Absorb everolimus-eluting bioresorbable vascular scaffold than with the Xience everolimus-eluting metallic stent during 2 years of prospective follow-up in the randomized AIDA trial.

AIDA (the Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial) was the first randomized trial designed to compare the Absorb scaffold to a drug-eluting metallic stent in a broad patient population reflecting routine real-world clinical practice. The disturbing AIDA finding follows upon earlier serious concerns raised regarding an increased risk of scaffold thrombosis – and the particularly worrisome complication of late thrombosis – in the ABSORB Japan and ABSORB II trials, Joanna J. Wykrzykowska, MD, reported at the annual congress of the European Association of Percutane-

ous Cardiovascular Interventions.

Importantly, the AIDA investigators could not identify any predictors of increased device thrombosis risk in Absorb recipients other than the device itself. Neither age, presenting symptoms, lesion characteristics, vessel size, cardiovascular risk factors, nor residual percentage stenosis defined a subgroup of scaffold recipients at particularly increased risk for this complication, said Dr. Wykrzykowska of the University of Amsterdam.

The device was approved by the Food and Drug Administration in July 2016. In March 2017 the agency issued a safety alert regarding the Absorb scaffold after release of the 2-year data from the 2,008-patient ABSORB III trial showing a significantly higher rate of target-lesion failure than with the Xience stent. Both devices are marketed by Abbott Vascular.

AIDA was a single-blind multicenter Dutch trial that randomized 1,845 patients undergoing PCI, 55% of whom presented with acute cor-

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NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA, compared with none in placebo. Consider varicella vaccination, if medically appropriate, prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions ($\geq 3\%$ and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasms, 3% (<1%).

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

Benefits of NUCALA:

- **SIGNIFICANTLY REDUCED EXACERBATIONS* BY 53%** in the MENSA trial (NUCALA: 0.83/year vs placebo: 1.74/year; $P < 0.001$)¹
- **SIGNIFICANTLY REDUCED DAILY OCS DOSE WHILE MAINTAINING ASTHMA CONTROL**, in the SIRIUS trial (vs placebo; $P = 0.008$)²
- **IMPROVED QUALITY OF LIFE** in the MENSA trial (SGRQ responder rate: NUCALA, 71%, vs placebo, 55%; odds ratio: 2.1; 95% CI: 1.3, 3.2)[†]

Statistical hierarchy was not met; endpoint is exploratory and results are descriptive only.³

MENSA (Trial 2)¹: 32-week study comparing treatment with NUCALA or placebo, added to regular treatment with high-dose ICS and at least 1 other controller with or without OCS, in 576 patients with severe asthma with an eosinophilic phenotype.[‡]

Primary endpoint: Frequency of exacerbations.

SIRIUS (Trial 3)²: 24-week study comparing treatment with NUCALA or placebo in 135 patients with severe asthma with an eosinophilic phenotype[‡] who required at least 5 mg to 35 mg of prednisone equivalent per day in addition to regular use of high-dose ICS plus an additional controller.

Primary endpoint: Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control.

ICS=inhaled corticosteroid; OCS=oral corticosteroid; SGRQ=St. George's Respiratory Questionnaire.

*Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients on maintenance oral/systemic corticosteroids, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

†The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response was defined as a reduction in score of 4 points or more.⁴

‡Identified by blood eosinophil counts ≥ 150 cells/ μ L at initiation of treatment (within 6 weeks of dosing) or ≥ 300 cells/ μ L in the past 12 months.

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothersbaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as the pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters.

References: **1.** Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. **2.** Bel EH, Wenzel SE, Thompson PJ, et al; for the SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371(13):1189-1197. **3.** Data on file, GSK. **4.** Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J.* 2002;19(3):398-404.

Please see Brief Summary of Prescribing Information for NUCALA on the following pages.

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Nucala[®]
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA® (mepolizumab) for injection, for subcutaneous use

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. [See *Clinical Studies (14) of full prescribing information.*]

Limitations of Use

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued [see *Contraindications (4)*].

5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [see *Adverse Reactions (6.1)*]. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Opportunistic infections: herpes zoster [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation [see *Clinical Studies (14) of full prescribing information*]. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-term Safety

Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

6.2 Immunogenicity

Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC [see *Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5-deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see *Use in Specific Populations (8.1)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. [See *Clinical Studies (14) of full prescribing information.*] Subjects had a reduction in the rate of exacerbations

8.4 Pediatric Use (cont'd)

that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies [see *Adverse Reactions* (6.1)].

8.5 Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

17. PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothersbaby.org/asthma [see *Use in Specific Populations* (8.1)].

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NCL:2BRS

New-onset AF after AVR did not affect long-term survival

BY MARK S. LESNEY

Frontline Medical News

New-onset atrial fibrillation after aortic valve replacement was not an independent risk factor for decreased long-term survival, according to the results of a single-center, retrospective study reported by Ben M. Swinkels, MD, of St. Antonius Hospital, Nieuwegein, and his colleagues in the Netherlands.

Key to this success, however, is restoring normal sinus rhythm before hospital discharge, they said.

In this retrospective, longitudinal cohort study, 569 consecutive patients with no history of AF who underwent AVR with or without concomitant coronary artery bypass grafting during 1990-1993 were followed for a mean of 17.8 years (*J Thorac Cardiovasc Surg.* 2017;154:492-8).

Thirty-day and long-term survival rates were determined in the 241 patients (42%) with and the 328 patients (58%) without new-onset postoperative atrial fibrillation (POAF), which was defined as electrocardiographically documented AF lasting for at least several hours, and occurring after AVR while the patient was still admitted. Standard therapy to prevent new-onset POAF was the use of sotalol in patients who were not on beta-blocker therapy, and continuation of beta-blocker therapy for those who were already on it.

There were no significant differences between the two groups in demographic characteristics. There were also no significant differences between the two groups in operative characteristics, postoperative in-hospital adverse events, and postoperative hospital lengths of stay until discharge home, except for mechanical ventilation time, which was significantly longer in the patients with new-onset POAF ($P = .011$).

Thirty-day mortality was 1.2% in the patients with POAF, and 2.7% in those without, a non-significant difference. There was no statistically

significant difference between the two survival curves. The Kaplan-Meier overall cumulative survival rates at 15 years of follow-up in the patients with new-onset POAF vs. those without were not statistically different (41.5% vs. 41.3%, respectively).

In addition, the 18-year probability of long-term first adverse events, including recurrent AF, transient ischemic attack, ischemic or hemorrhagic stroke, peripheral venous thromboembolism, or major or minor bleeding was not significantly different between the two groups.

“New-onset POAF after AVR does not affect long-term survival when treatment is aimed to restore sinus rhythm before the patient is discharged home. Future studies with a prospective, randomized design should be done to confirm this finding in patients undergoing different kinds of cardiac surgery,” the researchers concluded.

The study was funded by the authors’ home institution; the authors reported they had nothing to disclose.

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VIEW ON THE NEWS

Results contradict previous studies, but can still reassure

The incidence of atrial fibrillation after valve surgery has been described to be as high as 50%, Manuel J. Antunes, MD, said in an editorial commentary. “The adverse effect on long-term survival may not be related to the short-lived new-onset AF but rather to the underlying pathology associated to the arrhythmia, especially pathology that affects the myocardium, principally in atherosclerotic coronary artery disease,” he wrote. “It is not survival alone, however, that should be cause for concern; AF, even in episodes of limited duration, may result in transient ischemic attacks, ischemic, or hemorrhagic strokes, and peripheral thromboembolism, which is why affected patients should immediately be anticoagulated.” This study, however, is at odds with previously published studies, with opposite conclusions, according to Dr. Antunes. Swinkels and his colleagues suggest that one of the reasons for the discrepancy was the homogeneous character of their series, which consisted almost entirely

of patients who had isolated AVR. Dr. Antunes also adds that another important aspect to consider is that the antiarrhythmic drugs used prophylactically or therapeutically for this patient cohort (treated during 1990-1993) are no longer used or have been replaced by new and more efficacious pharmacologic agents.

“This contribution from Swinkels and colleagues reassures us that new-onset AF, common after heart surgery, may have no significant impact on early and late survival if sinus rhythm is effectively and permanently restored early after the onset of the arrhythmia and before the patient’s discharge from the hospital.”

Manuel J. Antunes, MD, of the University Hospital and Faculty of Medicine, Coimbra, Portugal, made these remarks in an invited editorial (J Thorac Cardiovasc Surg. 2017;154:490-1). He reported having nothing to disclose.



Continued from page 47

onary syndrome, and 26% of whom had ST-elevation MI. The primary endpoint was target vessel failure, a composite of cardiac death, target vessel MI, or target-vessel revascularization. The 2-year cumulative rate did not differ significantly between the two study arms: 11.7% in the scaffold group and 10.7% in the metallic stent recipients.

However, definite or probable device thrombosis occurred in 3.5% of the scaffold group compared with 0.9% of metallic stent recipients, for a highly significant 3.9-fold increased risk. This was associated with a significantly increased 2-year cumulative risk of MI: 5.5% versus 3.2%.

On the basis of this unsettling finding, coupled with the fact that ABSORB II investigators did not find any instance of very late scaffold thrombosis among 63 patients who remained on dual-antiplatelet therapy (DAPT)



Dr. Joanna J. Wykrzykowska

continuously for up to 3 years, Dr. Wykrzykowska and her coinvestigators have informed AIDA participants of their treatment assignment. They have also recommended that the Absorb recipients go on extended DAPT, even though there is no high-grade evidence as yet that this will prevent late scaffold thrombosis or that the

drug-induced increased bleeding risk of prolonged DAPT might cancel or perhaps even outweigh the potential protection against device thrombosis.

On top of all this, implantation of the scaffold entails a longer procedure time and a greater volume of contrast material.

Discussant Mahmoud Hashemian, MD, observed that, while bioresorbable vascular scaffolds are “physiologically ideal” because – unlike metallic stents – theoretically they leave no permanent implant to impede vasomotion and serve as a nidus for neoatherosclerosis, to date they have shown no real-world benefits over current-generation drug-eluting metallic stents, but only disadvantages.

“This doesn’t mean we have to feel hopeless. I’m not hopeless at all,” said Dr. Hashemian, an interventional cardiologist at Day General Hospital in Tehran. “I’m sure this [bioresorbable scaffolds] will be the future of our

stents. But it needs more work. The company tells me they are going to launch a newer one, maybe next year, with thinner struts and more expandability.”

Asked about the likely mechanism of prolonged thrombosis risk with Absorb, Dr. Wykrzykowska was quick to say no one really knows at this point.

“Technique [predilatation at a 1:1 balloon-to-artery ratio with an appropriately sized balloon] can obviously improve things in the short term for early events, but I don’t think we understand the biology of late events. We don’t understand the interaction between the device and the vessel. It’s extremely complex,” she said.

AIDA was funded by an unrestricted educational grant from Abbott Vascular. Dr. Wykrzykowska reported receiving consulting and lecture fees from the company.

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Preventive upstream therapy curbs atrial fib progression

BY BRUCE JANCIN

Frontline Medical News

BARCELONA – Aggressive treatment of known risk factors for atrial fibrillation resulted in improved 1-year maintenance of sinus rhythm in patients with recent-onset atrial fibrillation and heart failure in the randomized multicenter RACE 3 trial, Isabelle C. van Gelder, MD, reported at the annual congress of the European Society of Cardiology.

“We now screen for AF, making it possible to catch patients early. That’s what we’ve learned from this trial: If we start treating patients after their first episode of AF and aggressively reduce risk factors for AF, it may help the sinus rhythm. I think that’s an important message: Do not wait too long; start treatment early,” said Dr. van Gelder, professor of cardiology at the University of Groningen (the Netherlands).

She calls the interventional strategy tested in RACE 3 “risk factor-driven upstream therapy.” The four-pronged strategy consisted of statin therapy, a mineralcorticoid receptor antagonist, an ACE inhibitor and/or an angiotensin receptor blocker, and a 9- to 11-week supervised cardiac rehabilitation program emphasizing lifestyle modification through physical training and dietary changes supported by professional counseling to promote adherence.

RACE 3 (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure 3) was a multicenter, randomized, nonblinded clinical trial including 245 patients with, on average, a 3-month history of AF, a 2-month history of persistent AF, and a 2-month history of mild to moderate heart failure, either with preserved or reduced ejection fraction. All participants received guideline-directed rhythm control and heart failure therapies. In addition, half of participants were randomized to the upstream intervention. Three weeks after enrollment, all patients underwent electrical cardioversion.

The primary outcome was maintenance of sinus rhythm at 1 year as determined by 7-day Holter monitoring analyzed in blinded fashion at a central laboratory. The rate was 75% in the upstream intervention group, significantly better than the 63% in controls. This represented a 76% greater likelihood of sinus rhythm at 1 year in the upstream intervention

group. They also showed significant reductions in systolic and diastolic blood pressure, N-terminal pro-brain natriuretic peptide, and LDL cholesterol, compared with controls. However, at 1 year, the two groups didn’t

differ significantly in body mass index or left atrial volume.

The lack of impact on left atrial volume was disappointing, Dr. van Gelder said.

The RACE 3 trial was supported

by the Netherlands Heart Foundation and the Netherlands Heart Institute. Dr. van Gelder reported having no relevant financial interests.

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SYMBICORT 160/4.5 for the maintenance treatment of COPD

BETTER BREATHING^{*} WITH FAST CONTROL[†]



SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

#1 ICS/LABA PRESCRIBED
BY PULMONOLOGISTS
for new patients^{‡4}

^{*}Sustained improvement in lung function was demonstrated in a 12-month efficacy and safety study.^{1,2}

[†]In a serial spirometry subset of patients taking SYMBICORT 160/4.5 (n=121) in the SUN Study, 67% of 1-hour postdose FEV₁ improvement occurred at 5 minutes on day of randomization, 83% at month 6, and 84% at end of treatment.^{1,3}

[‡]Based on IMS data of prescriptions for new patients from March 2015 through February 2016.
See SUN Study design on next page.

⁴The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

- » **WARNING:** Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA
- » SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- » SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- » Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- » Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- » Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids
- » Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- » It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids
- » Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- » As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- » Immediate hypersensitivity reactions may occur as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.



Symbicort[®]
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol

A reassuring sense of control

Cancer screening in elderly: When to just say no

BY BRUCE JANCIN

Frontline Medical News

ESTES PARK, COLO. – A simple walking speed measurement over a 20-foot distance is an invaluable

guide to physiologic age as part of individualized decision making about when to stop cancer screening in elderly patients, according to Jeff Wallace, MD, professor of geriatric medicine at the University

of Colorado at Denver.

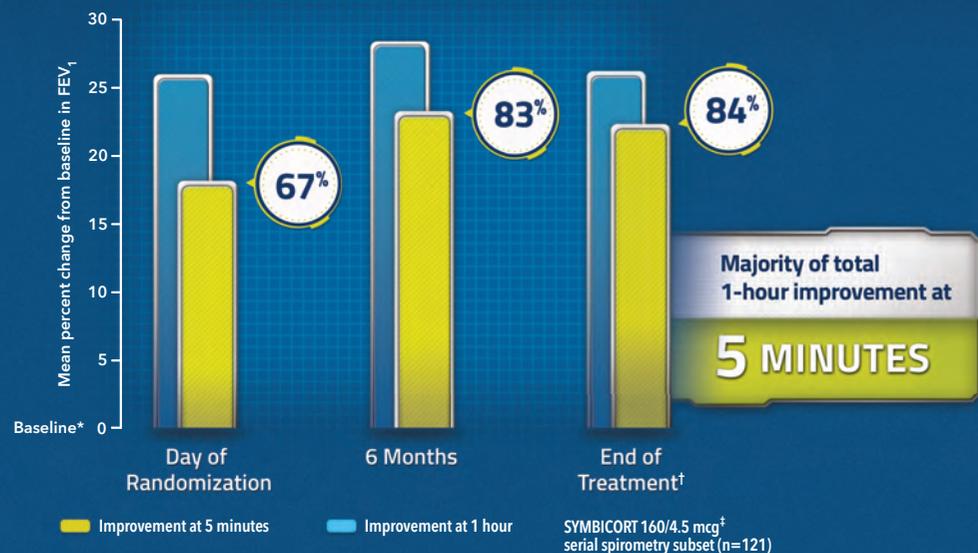
“If you have one measurement to assess ‘am I aging well?’ it’s your gait speed. A lot of us in geriatrics are advocating evaluation of gait speed in all patients as a fifth vital sign.

It’s probably more useful than blood pressure in some of the older adults coming into our clinics,” he said at a conference on internal medicine sponsored by the University of Colorado.

SYMBICORT 160/4.5 for the maintenance treatment of COPD

Fast control at 5 minutes each time^{1,2}

Percent of 1-hour improvement in FEV₁ occurring at 5 minutes over the 12-month study (serial spirometry subset)²



SUN: A 12-month efficacy and safety study: A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=494), SYMBICORT pMDI 80/4.5 mcg (n=494), formoterol 4.5 mcg (n=495), and placebo (n=481), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥ 10 pack-years, aged ≥ 40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 12-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV₁ and in 1-hour postdose FEV₁. The prespecified primary comparisons for predose FEV₁ were vs placebo and formoterol and the primary comparison for 1-hour postdose was vs placebo.

*Baseline is defined as the predose FEV₁ value on the day of randomization.

†Month 12, last observation carried forward (LOCF).

‡Administered as 2 inhalations twice daily.

COMPARATOR ARMS: Mean improvement in 1-hour postdose FEV₁ (mL/%) over 12 months (serial spirometry subset)

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%).

6 Months: SYMBICORT 160/4.5 mcg (270 mL/28%), formoterol 4.5 mcg (200 mL/23%), placebo (60 mL/7%).

End of month 12 (LOCF): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%).

SYMBICORT 160/4.5 mcg[†] (n=121), formoterol 4.5 mcg[†] (n=124), placebo[†] (n=125).

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING (cont'd)

- » Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- » Long-term use of orally inhaled corticosteroids may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- » Glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- » In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions
- » SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- » Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- » The most common adverse reactions $\geq 3\%$ reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- » SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents

Dr. Wallace also gave a shout-out to the ePrognosis cancer-screening decision tool, available free at www.eprognosis.org, as an aid in shared decision-making conversations regarding when to stop cancer screening. This tool, developed by researchers at the University of California, San Francisco, allows physicians to plug key individual patient characteristics into its model, including comorbid conditions,

functional status, and body mass index, and then spits out data-driven estimated benefits and harms a patient can expect from advanced-age screening for colon or breast cancer.

Of course, guidelines as to when to stop screening for various cancers are available from the U.S. Preventive Services Task Force, the American Cancer Society, and specialty societies. However, it's important

that nongeriatricians understand the serious limitations of those guidelines.

"We're not guidelines followers in the geriatrics world because the guidelines don't apply to most of our patients," he explained. "We hate guidelines in geriatrics because few studies – and no lung cancer or breast cancer trials – enroll patients over age 75 with comorbid conditions.

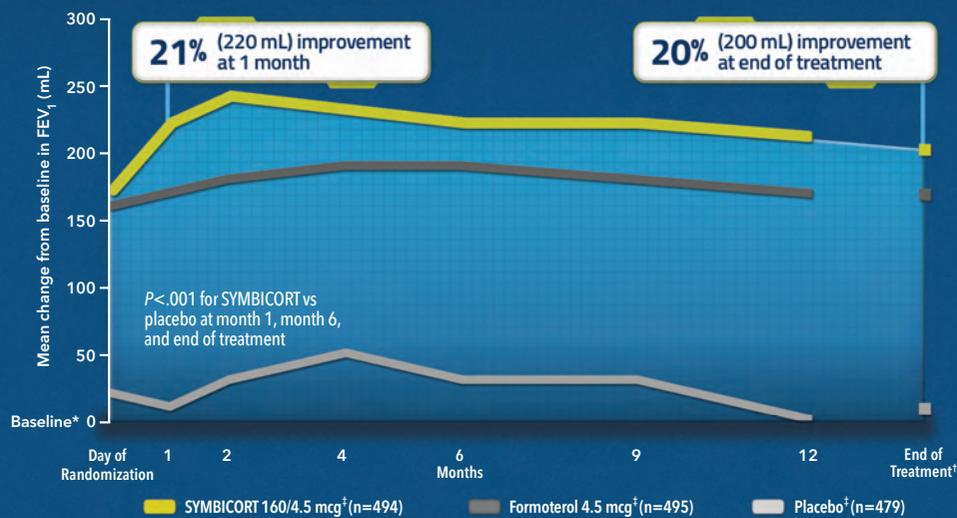


DR. WALLACE

Continued on following page

Sustained effect. Control over 12 months.^{1,2}

Improvement in 1-hour postdose FEV₁ over the 12-month study²



» SYMBICORT 160/4.5 significantly improved predose FEV₁ averaged over the course of the study compared to placebo and formoterol, a coprimary endpoint¹

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

COMPARATOR ARMS: Mean improvement in 1-hour postdose FEV₁ (mL/%) over 12 months

1 Month: SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%).

6 Months: SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (190 mL/18%), placebo (30 mL/3%).

End of treatment: SYMBICORT 160/4.5 mcg (200 mL/20%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%).

SYMBICORT 160/4.5 mcg[†] (n=494), formoterol 4.5 mcg[†] (n=495), placebo[†] (n=479).

*Baseline is defined as the predose FEV₁ value on the day of randomization.

[†]Month 12, last observation carried forward (LOCF).

[‡]Administered as 2 inhalations twice daily.

See SUN Study design on left page.



- » Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- » ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

- » SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
- » SYMBICORT is NOT indicated for the relief of acute bronchospasm

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. 2. Data on File, 1084400, AZPLP. 3. SYMBICORT [Package Insert]. Wilmington, DE: AstraZeneca; 2016. 4. Data on File, 3255902, AZPLP.

AstraZeneca

Symbicort
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol
A reassuring sense of control

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Also, most of these guidelines do not incorporate patient preferences, which probably should be a primary goal. So we're left extrapolating."

Regrettably, though, "it turns out most Americans are drinking the Kool-Aid when it comes to patient preferences. It's amazing how much cancer screening is going on in this

country. We're doing a lot more than we should," said Dr. Wallace.

He highlighted a University of North Carolina study of more than 27,000 participants aged 65 years or older in the population-based National Health Interview Survey. Among those deemed at very high risk of mortality within 9 years, 55% of men had recently under-

gone prostate cancer screening, and 53% of women had recently had a mammogram. Up to 56% of women who underwent a hysterectomy for benign reasons had a Pap test within the previous 3 years. Moreover, more than one-third of women with less than a 5-year life expectancy had a recent mammogram (JAMA Intern Med. 2014

Oct;174[10]:1558-65).

All of that is clearly overscreening. Experts unanimously agree that, if someone is not going to live for 10 years, the person is not likely to benefit from cancer screening. The one exception is lung cancer screening of high-risk patients, where there are data to show that annual low-dose CT screening is beneficial

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
For full Prescribing Information, see package insert.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [see Warnings and Precautions (5.1)].

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see Warnings and Precautions (5.1) in the full Prescribing Information]. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only strength indicated for the treatment of airflow obstruction in COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABA, including formoterol, one of the active ingredients in SYMBICORT. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment

regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of SYMBICORT and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled drugs containing beta₂-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Pneumonia and Other Lower Respiratory Tract Infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6-month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1%) compared with placebo (1.3%). In a 12-month study of 1,964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta₂-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing

in those with even a 5-year life expectancy.

As part of the Choosing Wisely program, the American Geriatric Society has advocated that physicians “don’t recommend screening for breast, colorectal, prostate, or lung cancer without considering life expectancy and the risks of testing, overdiagnosis, and overtreatment.”

That’s where gait speed and ePrognosis come in handy in discussions with patients regarding what they can realistically expect from cancer screening at an advanced age.

The importance of gait speed was highlighted in a pooled analysis of nine cohort studies totaling more than 34,000 community-dwelling adults aged 65 years and older with

6-21 years of follow-up. Investigators at the University of Pittsburgh identified a strong relationship between gait speed and survival. Every 0.1-m/sec made a significant difference (JAMA. 2011 Jan 5;305[1]:50-8).

A gait speed evaluation is simple: The patient is asked to walk 20 feet at a normal speed, not racing. For

men age 75, the Pittsburgh investigators found, gait speed predicted 10-year survival across a range of 19%-87%. The median speed was 0.8 m/sec, or about 1.8 mph, so a middle-of-the-pack walker ought to stop all cancer screening by age 75. A fast-walking older man won’t reach a 10-year remaining life

Continued on following page

SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol

2

the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

Paradoxical Bronchospasm and Upper Airway Symptoms

As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see *Overdosage (10) in the full Prescribing Information*]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter. If significant reductions in BMD are seen and SYMBICORT is still considered medically important for that patient’s COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient’s dose to the lowest dosage that effectively controls his/her symptoms [see *Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information*].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see *Clinical Pharmacology (12.2) in the full Prescribing Information*]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see *Warnings and Precautions (5.1) in the full Prescribing Information*].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see *Warnings and Precautions (5.4) in the full Prescribing Information*]
- Pneumonia or lower respiratory tract infections in patients with COPD [see *Warnings and Precautions (5.5) in the full Prescribing Information*]
- Immunosuppression [see *Warnings and Precautions (5.6) in the full Prescribing Information*]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions (5.8) in the full Prescribing Information*]
- Growth effects in pediatric patients [see *Warnings and Precautions (5.14) in the full Prescribing Information*]
- Glaucoma and cataracts [see *Warnings and Precautions (5.15) in the full Prescribing Information*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV₁ at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

expectancy until he's in his early to mid-80s; a slow walker reaches that life expectancy as early as his late 60s, depending upon just how slow he walks. A woman at age 80 with an average gait speed has roughly 10 years of remaining life, factoring in plus or minus 5 years from that landmark depending

upon whether she is a faster- or slower-than-average walker, Dr. Wallace explained.

The U.S. Preventive Services Task Force currently recommends colon cancer screening routinely for 50- to 75-year-olds, declaring in accord with other groups that this strategy has a high certainty of substantial net benefit. But the USPSTF also

recommends selective screening for those aged 76-85, with a weaker C recommendation (JAMA. 2016 Jun 21;315[23]:2564-75).

What are the practical implications of that recommendation for selective screening after age 75?

Investigators at Harvard Medical School and the University of Oslo recently took a closer look. Their

population-based, prospective, observational study included 1,355,692 Medicare beneficiaries aged 70-79 years at average risk for colorectal cancer who had not had a colonoscopy within the previous 5 years.

The investigators demonstrated that the benefit of screening colonoscopy decreased with age. For patients aged 70-74, the 8-year risk of colorectal cancer was 2.19% in those who were screened, compared with 2.62% in those who weren't, for an absolute 0.43% difference. The number needed to be screened to detect one additional case of colorectal cancer was 283. Among those aged 75-79, the number needed to be screened climbed to 714 (Ann Intern Med. 2017 Jan 3;166[1]:18-26).

Moreover, the risk of colonoscopy-related adverse events also climbed with age. These included perforations, falls while racing to the bathroom during the preprocedural bowel prep, and the humiliation of fecal incontinence. The excess 30-day risk for any adverse event in the colonoscopy group was 5.6 events per 1,000 patients aged 70-74 and 10.3 per 1,000 in 75- to 79-year-olds.

In a similar vein, Mara A. Schonberg, MD, of Harvard Medical School, Boston, has shed light on the risks and benefits of biannual mammographic screening for breast cancer in 70- to 79-year-olds, a practice recommended in American Cancer Society guidelines for women who are in overall good health and have at least a 10-year life expectancy.

She estimated that 2 women per 1,000 screened would avoid death due to breast cancer, for a number needed to screen of 500. But roughly 200 of those 1,000 women would experience a false-positive mammogram, and 20-40 of those false-positive imaging studies would result in a breast biopsy. Also, roughly 30% of the screen-detected cancers would not otherwise become apparent in an older woman's lifetime, yet nearly all of the malignancies would undergo breast cancer therapy (J Am Geriatr Soc. 2016 Dec;64[12]:2413-8).

Dr. Schonberg's research speaks to Dr. Wallace.

"It's breast cancer therapy: It's procedures; it's medicalizing the patient's whole life and creating a high degree of angst when she's 75 or 80," he said.

Dr. Wallace reported having no financial conflicts regarding his presentation.

bjancin@frontlinemedcom.com

SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol

3

Table 1 Adverse reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment/ Adverse Event	SYMBICORT		Budesonide		Formoterol		Placebo
	80/4.5 N = 277	160/4.5 N = 124	80 mcg N = 121	160 mcg N = 109	4.5 mcg N = 237	N = 400	
	%	%	%	%	%	%	%
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0	
Headache	6.5	11.3	11.6	12.8	8.9	6.5	
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8	
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8	
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8	
Influenza	3.2	2.4	6.6	0.9	3.0	1.3	
Back pain	3.2	1.6	2.5	5.5	2.1	0.8	
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0	
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8	
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0	
Oral Candidiasis	1.4	3.2	0	0	0	0.8	
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9	

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of $\geq 3\%$ and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV₁ at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of $\geq 3\%$ in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment/ Adverse Event	SYMBICORT	Budesonide	Formoterol	Placebo
	160/4.5 N = 771	160 mcg N = 275	4.5 mcg N = 779	N = 781
	%	%	%	%
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	255.2	157.1	240.3	223.7

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta₂-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) [see Warnings and Precautions (5.9) in the full Prescribing Information].

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see Warnings and Precautions (5) in the full Prescribing Information]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta₂-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

SYMBICORT is a trademark of the AstraZeneca group of companies.

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By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France

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An interview with incoming CHEST President, John Studdard, MD, FCCP

Born and raised in Mississippi, Dr. Studdard says there were four factors that inspired him to become a physician:

1. I have always loved people and working with them, and I always admired the respect that physicians received in my community.
2. We generally enjoy doing what we are pretty good at...I am pretty good at math and science, and these were important components in pre-med curriculum in my day.
3. I am competitive and decided if it was going to be hard to get into medical school, then I wanted to go to medical school.
4. My dad always told my brother and me that we would be doctors when we grew up, because we were going to be our own boss. I have been in private practice for 36 years, and that is not the case, not if you are doing it right. I obviously love medicine, and my dad was great in that he paid for our education...but he called the shots.

What are some of the biggest challenges you have encountered throughout your career?

Private practice makes you gain more independence and autonomy; you have to become more agile, more efficient, and you have awfully big workloads. However, you give up the academic stimulation of being in an academic center. It is a tough discipline in the private practice of medicine to try to stay up to date. Whether going to the CHEST Annual Meeting, reading our journal *CHEST*, or looking at CHEST education online products, those of us in the clinical practice of pulmonary, critical care, and sleep medicine are more dependent than any group on what our clinical educators write and teach.

How do/did you balance work and your personal life?

We are busy in practice, particularly when taking on volunteer opportunities, and that time comes out of something: time with family, hobbies, it has to come from somewhere. But it is not unique to those of us in medicine. My daughter is a 33-year-old mother to a 20-month-old beautiful granddaughter of ours and is pregnant with another child, and she and her husband both work full time. Our son and his wife also both work and must find ways to balance work/life issues.

So work-life balance, particularly in today's world, is more difficult than ever for everyone. I am blessed that my wife is the daughter of a general surgeon, and she understood a little bit about stressors in a physician's life – sometimes she seems to understand more than others—she is a unique person. Work-life balance is all about priorities – our priority was our family. We spent a ton of time with our children, great vacations, rarely missed a program or ballgame (there were lots of them), and frequently that involved going to work early in the morning, coming home early in the evening, and going back to the hospital to finish up late at night. A lot of being a good parent is being lucky. We either did a lot of things right, or were lucky, or a combination of both, because I think our kids turned out pretty darn well.

What has been your favorite project throughout your involvement with CHEST?

Early in my days as a member of CHEST, a mentor of mine from training at the Mayo Clinic, Dr. Doug Gracey, gave me the opportunity to join the CHEST Government Relations Committee, which he chaired. After a few years, I was given the opportunity to serve as its Chair. We became heavily involved in the tobacco wars, as some people called them. Our Attorney General in Mississippi at the time, Mike Moore, and a plaintiff's attorney in Mississippi, Dick Scruggs, whom I knew from some work I had done from the defense side of asbestos litigation, took a lead role in the Attorney General's Master Settlement – a group of attorney generals suing the tobacco industry (basically, state's Medicaid was suing the tobacco industry for reimbursement of funds). It was a completely different approach. The tobacco industry turned its nose up at it at first – they did not think it had a chance to fly, but it did. CHEST got involved early on, and then a big group of people, including Tobacco Free Kids, the American Cancer Society, and many others in the public health space, got involved. CHEST represented the public health community during part of the negotiations that led to the Attorney General's Master Settlement. We should be very proud of the role CHEST played in this critical public health effort. If I can look back at my time spent in CHEST leadership, and see it as fond-

ly as I do when I look back at my time just being a part of our CHEST Foundation, I will feel incredibly fulfilled.

What made you want to be President of CHEST?

I believe it is always important to give back to the people who gave you something. CHEST has given me a ton over the last 36 years, so giving back to CHEST is easy.

What are you looking forward to as President of CHEST?

On a personal level, I am looking forward to what we are doing right now, meeting new people, and learning from young people.

Because of my background and upbringing, I have a passion for diversity and inclusion; I think we need to continue to talk about, learn about, care about, be open about, and be transparent about diversity of thought, inclusion, and care disparity. The word “diversity” means something different to every person, and for that, we have to have respect.

Continued on page 62



John Studdard, MD, FCCP, has been a member of the American College of Chest Physicians for 36 years, and, this November, he will be inaugurated as CHEST President. This will not be Dr. Studdard's first time in a presidential role for CHEST, as he served as CHEST Foundation President in 2013 and 2014. Currently, Dr. Studdard serves as a pulmonologist at Jackson Pulmonary in Jackson, Mississippi. Being a physician and being as heavily involved with an organization as Dr. Studdard is takes a lot of prioritizing, hard work, and dedication. Get to know CHEST's new President through this interview.

CHEST
Annual Meeting
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TORONTO
CANADA
October 28 - November 1



CHEST 2017 Early Education Opportunities

Planning on arriving to Toronto a day early? Attend one of our postgraduate course tracks happening Saturday, October 28. (Full- and half-day options available.)

- Topics include:**
- Thoracic Ultrasound
 - Pulmonary Medicine Literature Review and Update
 - Critical Care: Things Your Fellows Do But You Might Not
 - Interstitial Lung Disease
 - Sleep Medicine: Board Review

Seats are filling quickly, reserve yours today. chestmeeting.chestnet.org

#Winning: Are you in it to win it at CHEST 2017?

CHEST 2017 offers several contests and opportunities to win great prizes! Are you ready to take home the prize?

CHEST Events App Game: Click Game

Do you like scavenger hunts? How about prizes? In our CHEST Events app, you will find the game Click filled with a list of photo challenges. To participate, simply log in and earn your challenge badges by

CHEST Annual Meeting 2017

submitting photos to your profile. As you complete each challenge throughout the duration of CHEST 2017, your badges will accumulate, and we will award sweet treats to the person(s) with the highest number of badges on the last day of the annual meeting. Winners can stop by the press room, Metro Toronto Convention Centre, **Room 706**, to collect prizes on Wednesday, November 1, by 2:00 PM local time.

Rules of participation

- To participate, you must be a registered attendee on-site at CHEST 2017.
- The contest begins Saturday, October 28 at 12:00 PM EST, and ends Wednesday, November 1, at 10:00 AM EST.
- Prize must be picked up in the Press Room, **Room 706**, between the hours of 10:00 AM and 2:00 PM, November 1.
- Questions about the Click photo contest should be directed to socialmedia@chestnet.org

Are you a VITweep?

Get active on Twitter, and share your latest highlights for #CHEST2017! Sitting in on an interesting session? Having a great time visiting the posters? Let us know! The most active tweeters for the day will receive a special prize!

Share your selfies!

See a selfie spot and take advantage of it! We know there's more to your trip than lectures and keynote speakers, and we want to see it!

Throughout the convention center, you'll find many designated areas to snap and share photos of yourself and

colleagues! Be sure to find them all and share your images on Twitter or Instagram using our #CHEST2017 hashtag. We'll choose our favorite photo of the day and reshare your pic-

ture with our social media followers. Don't miss your chance to be featured!

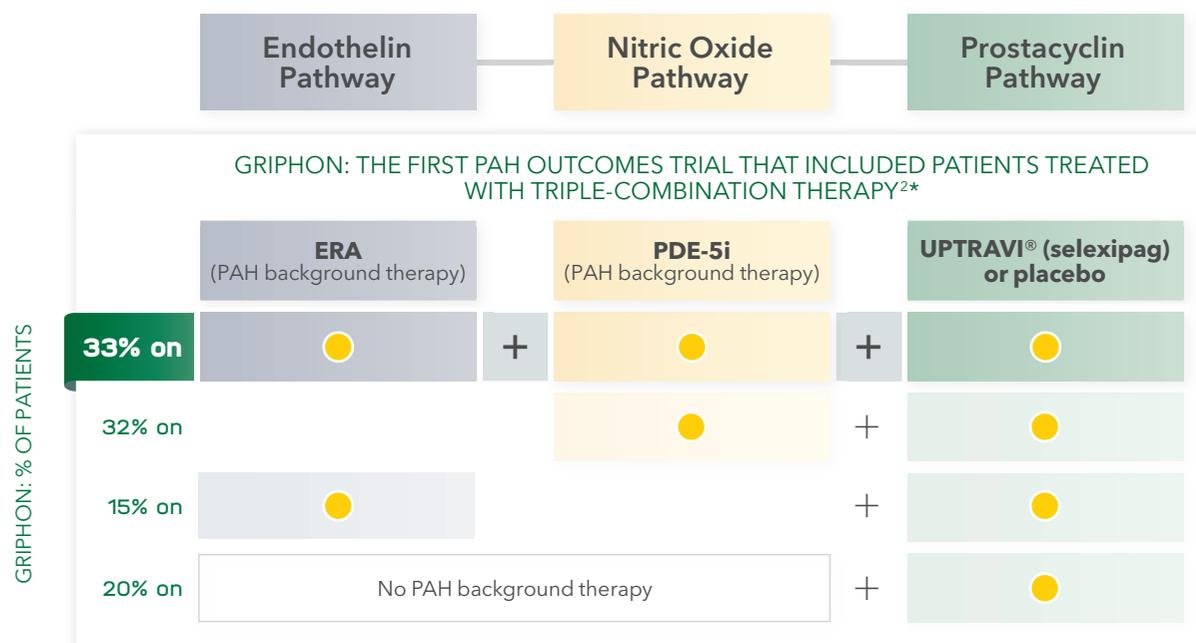
Don't miss out on CHEST Bingo

Take advantage of one of the many

opportunities in the Exhibit Hall during CHEST. Play CHEST Bingo daily, starting Monday, October 30, through Wednesday, November 1, for a chance to win a prize!

IN PAH (WHO GROUP I), 3 Key Pathways Are Targeted for Treatment¹

Triple UP
3 Oral Therapies for 3 Pathways



Study description: GRIPHON was a multicenter, long-term, double-blind, placebo-controlled, parallel-group, event-driven phase 3 study in patients (UPTRAVI: n=574; placebo: n=582) with symptomatic PAH (nearly all WHO FC II-III at baseline). The median duration of exposure to UPTRAVI was 1.4 years.

- 2015 ESC/ERS Guidelines recommend UPTRAVI added to ERA and/or PDE-5i for efficacy of sequential combination therapy in FC II and FC III PAH (WHO Group I)³

INDICATION

UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (eg, gemfibrozil) with UPTRAVI is contraindicated.

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

ADVERSE REACTIONS

Adverse reactions more frequent compared to placebo (≥3%) are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

DRUG INTERACTIONS

CYP2C8 Inhibitors

Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant use of UPTRAVI with strong inhibitors of CYP2C8 is contraindicated.

Although not studied, use of UPTRAVI with moderate CYP2C8 inhibitors (eg, teriflunomide and deferasirox) can be expected to increase exposure to the active metabolite of selexipag. Consider a less frequent UPTRAVI dosing regimen, eg, once-daily, when initiating in patients on a moderate CYP2C8 inhibitor. Reduce UPTRAVI when initiating a moderate CYP2C8 inhibitor.

Please see additional Important Safety Information on adjacent page.

*UPTRAVI in combination with an ERA and PDE-5i.

How to play:

Find your bingo card in the program guide that you will receive during registration. Get each bingo letter to spell out C-H-E-S-T as you visit each of the five sponsors' booths. You will then have a chance to win a \$75 gift certificate to the

CHEST bookstore. There will be a winner drawn every night!

Win an iPad®!

This year, attendees will have the opportunity to win a refurbished iPad for playing one of our Simulation Center's arcade style GAMES (Games

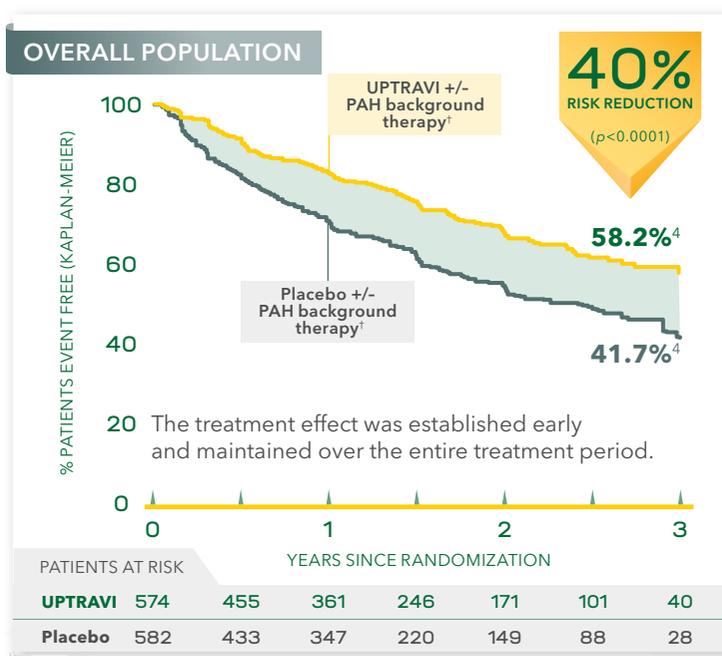
Augmenting Medical Education). Last year, we gave away 15 refurbished iPad 2s; this year, we hope to give away 30 refurbished iPad 2s! iPads will be awarded for the following:

- One each day for the fastest time on Aspirated!

- One each day for whoever has played the most games and Virtual Patient Tours (VPTs).
- Several for playing the games Peer Pressure and Nodal Nemesis. Please refer to the program schedule in the CHEST Events app for dates and times of the GAMES and VPTs.

Consistent Treatment Effect on Time to First Disease Progression Event, Irrespective of PAH Background Therapy²

PRIMARY ENDPOINT: TIME TO FIRST DISEASE PROGRESSION EVENT IN GRIPHON



A primary endpoint event was experienced by 27.0% (155/574) of UPTRAVI-treated patients vs 41.6% (242/582) of placebo-treated patients.

Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo):

- Hospitalization for PAH (13.6% vs 18.7%)
- Other disease progression events (6.6% vs 17.2%)[‡]
- Death (4.9% vs 3.1%)
- Initiation of parenteral prostanoid or chronic oxygen therapy (1.7% vs 2.2%)
- PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%)

Reductions in PAH-related hospitalization and other disease progression events[‡] drove an overall 40% risk reduction.

Add UPTRAVI to an ERA + PDE-5i for All-oral TRIPLE-combination Therapy

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS (cont'd)

CYP2C8 Inducers

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

Patients With Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Dosage Strengths

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg.

Please see Brief Summary of Prescribing Information on the following page.

[†]An ERA, PDE-5i, or both.

[‡]Other disease progression defined as a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

6MWD=6-minute walk distance; ERA=endothelin receptor antagonist; ERS=European Respiratory Society; ESC=European Society of Cardiology; PDE-5i=phosphodiesterase type-5 inhibitor; WHO=World Health Organization.

References: 1. Humbert M, Lau EM, Montani D, et al. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation*. 2014;130(24):2189-2208. 2. UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc. July 2017. 3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46(4):903-975. 4. Data on file, Actelion Pharmaceuticals.

Visit www.UPTRAVI.com/hcp to learn more



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Changes to CPT[®] codes coming January 2018

BY MIKE NELSON, MD, FCCP
CHEST Physician Editorial Board Member

There will be a number of changes to Current Procedural Terminology (CPT[®]) codes of interest to pulmonary/critical care providers in January 2018. A thorough understanding of these changes is important for appropriate coding and reimbursement for the services described by these codes.

There are two changes in the CPT codes for bronchoscopy involving **31645** and **31646**. CPT code **31645** describes a therapeutic bronchoscopy, eg, removal of viscous, copious or tenacious secretions from the airway. It had previously included wording that suggested it was used for abscess drainage, and this has been removed. If a therapeutic bronchoscopy procedure is repeated during the same hospital stay, then CPT code **31646** should be utilized. If a therapeutic bronchoscopy procedure is performed in the non-hospital setting and later repeated, then CPT code **31646** would be used for both procedures.

CPT code **94620** *Pulmonary stress testing; simple (eg, 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)* has been deleted and replaced by two new codes. CPT code **94617** *Exercise test for bronchospasm, including pre- and postspirometry, electrocardiographic recording(s), and pulse oximetry* describes the procedure used to assess for exercise-induced bronchospasm. CPT code **94618** *Pulmonary stress testing (eg, 6-minute walk test), including measurement of heart rate, oximetry, and oxygen titration, when performed*, describes the typical simple pulmonary stress test. After January 1, 2018, if CPT code **94620** is used, the claim will be denied. CPT code **94621** *Cardiopulmonary exercise testing, including measurements of minute ventilation, CO₂ production, O₂ uptake, and electrocardiographic recordings* has been reworded to better describe the procedure of cardiopulmonary exercise testing. Additionally, there are numerous parentheticals appended that list the CPT codes that may not be used in conjunction with **94617**, **94618**, and **94621**. Please refer to the 2018 CPT manual for further information on these exclusions.

CPT code **94620** *Pulmonary stress testing; simple (eg, 6-minute walk test, prolonged exercise test for bronchospasm with pre- and post-spirometry and oximetry)* has been deleted and replaced by two new codes. CPT code **94617** *Exercise test for bronchospasm, including pre- and postspirometry, electrocardiographic recording(s), and pulse oximetry* describes the procedure used to assess for exercise-induced bronchospasm. CPT code **94618** *Pulmonary stress testing (eg, 6-minute walk test), including measurement of heart rate, oximetry, and oxygen titration, when performed*, describes the typical simple pulmonary stress test. After January 1, 2018, if CPT code **94620** is used, the claim will be denied. CPT code **94621** *Cardiopulmonary exercise testing, including measurements of minute ventilation, CO₂ production, O₂ uptake, and electrocardiographic recordings* has been reworded to better describe the procedure of cardiopulmonary exercise testing. Additionally, there are numerous parentheticals appended that list the CPT codes that may not be used in conjunction with **94617**, **94618**, and **94621**. Please refer to the 2018 CPT manual for further information on these exclusions.

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UPTRAVI[®] (selexipag) Rx Only

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Please see full Prescribing Information.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

UPTRAVI[®] (selexipag) is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

CONTRAINDICATIONS

Concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) [see *Drug Interactions (CYP2C8 Inhibitors) and Clinical Pharmacology (Pharmacokinetics)*].

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of UPTRAVI has been evaluated in a long-term, placebo-controlled study enrolling 1156 patients with symptomatic PAH (GRIPHON study). The exposure to UPTRAVI in this trial was up to 4.2 years with median duration of exposure of 1.4 years. The following list presents adverse reactions more frequent on UPTRAVI (N=575) than on placebo (N=577) by $\geq 3\%$: headache 65% vs 32%, diarrhea 42% vs 18%, jaw pain 26% vs 6%, nausea 33% vs 18%, myalgia 16% vs 6%, vomiting 18% vs 9%, pain in extremity 17% vs 8%, flushing 12% vs 5%, arthralgia 11% vs 8%, anemia 8% vs 5%, decreased appetite 6% vs 3%, and rash 11% vs 8%.

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

Laboratory Test Abnormalities

Hemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from -0.34 to -0.02 g/dL in the selexipag group compared to -0.05 to 0.25 g/dL in the placebo group. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to -0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

DRUG INTERACTIONS

CYP2C8 Inhibitors

Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated [see *Contraindications and Clinical Pharmacology (Pharmacokinetics)*].

Although not studied, use of UPTRAVI with moderate CYP2C8 inhibitors (e.g., terfenadine and desferasirox) can be expected to increase exposure to the active metabolite of selexipag. Consider a less frequent dosing regimen, e.g., once-daily, when initiating UPTRAVI in patients on a moderate CYP2C8 inhibitor. Reduce UPTRAVI when a moderate CYP2C8 inhibitor is initiated.

CYP2C8 Inducers

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase dose up to twice of UPTRAVI when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped [see *Clinical Pharmacology (Pharmacokinetics)*].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures up to 50 times the human exposure at the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

Lactation

It is not known if UPTRAVI is present in human milk. Selexipag or its metabolites were present in the milk of rats. Because many drugs are present in the human

UPTRAVI[®] (selexipag) Rx Only

milk and because of the potential for serious adverse reactions in nursing infants, discontinue nursing or discontinue UPTRAVI.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older, while 19 were 75 and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity cannot be ruled out.

Patients with Hepatic Impairment

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C). Avoid use of UPTRAVI in patients with severe hepatic impairment [see *Clinical Pharmacology (Pharmacokinetics)*].

Patients with Renal Impairment

No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate >15 mL/min/1.73 m².

There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates <15 mL/min/1.73 m² [see *Clinical Pharmacology (Pharmacokinetics)*].

OVERDOSAGE

Isolated cases of overdose up to 3200 mcg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Specific Populations:

Hepatic Impairment:

In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, exposure to selexipag was 2- and 4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. [see *Use in Specific Populations*].

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, the exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in these patients during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice-daily regimen.

Renal Impairment:

A 40-70% increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate ≥ 15 mL/min/1.73 m² and < 30 mL/min/1.73 m²) [see *Use in Specific Populations*].

Drug Interaction Studies:

In vitro studies

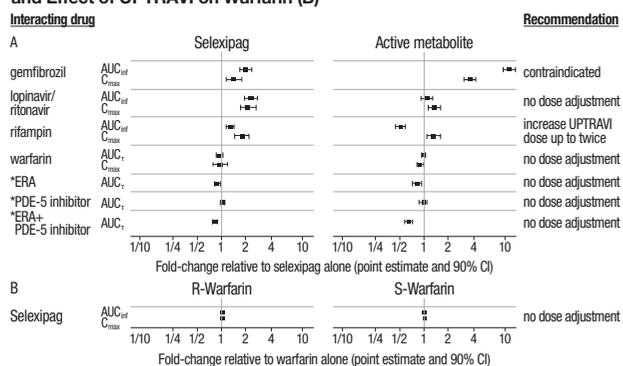
Selexipag is hydrolyzed to its active metabolite by carboxylesterases. Selexipag and its active metabolite both undergo oxidative metabolism mainly by CYP2C8 and to a smaller extent by CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP).

Selexipag and its active metabolite do not inhibit or induce hepatic cytochrome P450 enzymes at clinically relevant concentrations. Selexipag and its active metabolite do not inhibit hepatic or renal transport proteins.

The effect of moderate inhibitors of CYP2C8 on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with moderate inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite [see *Drug Interactions (CYP2C8 Inhibitors)*].

The results on in vivo drug interaction studies are presented in Figure 1.

Figure 1 Effect of Other Drugs on UPTRAVI and its Active Metabolite (A) and Effect of UPTRAVI on Warfarin (B)



*ERA and PDE-5 inhibitor data from GRIPHON.

Manufactured for: Actelion Pharmaceuticals US, Inc. 5000 Shoreline Court, Ste. 200, South San Francisco, CA 94080, USA ACT20170721

Reference: UPTRAVI full Prescribing Information.

Actelion Pharmaceuticals US, Inc. July 2017.

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NEW PRESIDENT // continued from page 59

As Dr. Studdard prepares to take on his new role in CHEST leadership this October, he is optimistic about what the future will bring and about the things that he will learn. He considers himself incredibly lucky to be in the position that he is in, and he values each relationship he has made during his involvement with CHEST. He is looking forward to all that is in store during his time as President. He left us with a quote from Wyatt Cooper: "The only immortality we can be sure of is that part of ourselves we invest in others—the contribution we make to the totality of man, the knowledge we have shared, the truths we have found, the causes we have served, the lessons we have lived."

NETWORKS

Transbronchial cryobiopsy, updated guidelines for chronic cough in children, PD-1 inhibition

Interventional Chest/ Diagnostic Procedures

Cryobiopsy for ILD: Careful stewardship needed

Interest in transbronchial cryobiopsy has accelerated rapidly in recent years. This procedure is performed by advancing a cryoprobe into the peripheral lung via flexible bron-



DR. LENTZ



DR. MALDONADO

choscopy, where lung tissue freezes and adheres to the probe and is subsequently extracted as a cryobiopsy. The number of cryobiopsy-related publications has increased exponentially since it was described in 2009 (Babiak A, et al. *Respiration*. 2009;78[2]:203). This interest stems from reports of high diagnostic yields in patients with interstitial lung disease (ILD) while maintaining complication rates similar to that of conventional bronchoscopic biopsy.

Traditional bronchoscopic biopsies are notoriously insensitive; a specific diagnosis can be established in fewer than a third of cases (Sheth JS, et al. *Chest*. 2017;151[2]:389). As such, surgical lung biopsy continues to be recommended but is associated with significant mortality (2%) and morbidity (30%) in patients with ILD (Hutchinson JP, et al. *ARJCCM*. 2016;193[10]:1161). Cryobiopsy, which appears to rival surgical lung biopsy in terms of ability to contribute to a specific diagnosis, is, therefore, a highly promising alternative (Tomassetti S, et al. *AJRCCM*. 2016;193[7]:745).

As cryobiopsy is increasingly adopted around the world, however, troubling reports of serious complications have surfaced. Most notable is the recently reported experience of the initial 25 cases performed at the University of Pennsylvania, in which almost one in four patients suffered serious complications

(DiBardino DM, et al. *Ann Am Thorac Soc*. 2017;14[6]:851). The authors pointed to lack of a pre-defined procedural protocol, as well as several choices relating to the specific technique used, including inconsistent use of fluoroscopy, lack of prophylactic bronchial blocker placement, and predominant use of laryngeal mask airways as potential contributing factors. Indeed, many variations of the basic cryobiopsy procedure have been described (Lentz RJ, et al. *J Thoracic Dis*. 2017;9[7]:2186), with no formal guidance or training available to inform advanced bronchoscopists interested in this procedure.

It is incumbent on the interventional pulmonology and ILD specialist communities to be responsible stewards of this promising procedure. Implementation of three parallel efforts to standardize and rigorously study this procedure should be considered as soon as possible: creation of expert consensus guidelines establishing best-practices for safe and effective biopsy technique; a training requirement before independent performance of the procedure; and creation of an international cryobiopsy registry to facilitate higher-quality research into optimal technique and outcomes. We owe this to our patients.

Robert J. Lentz, MD
NetWork Member

Fabien Maldonado, MD, FCCP
NetWork Member

Pediatric Chest Medicine

Chronic cough in children: New guidelines

A chronic cough is a common complaint among children whose parents seek medical evaluation. Chronic wet cough can indicate an underlying illness; therefore, an early diagnosis can lead to prevention of complications of the disease and improvement in quality of life.

CHEST is a leading resource in evidence and consensus-based guidelines on important topics affecting children. The most recent guidelines entitled Management of Children with Chronic Wet Cough and Protracted Bacterial Bronchitis

(*Chest*. 2017;151(4):884-890) and Use of Management Pathways or Algorithms in Children with Chronic Cough (*Chest*. 2017;151(4):875-873) are updates from the 2006 CHEST guidelines on chronic cough in children.

The present updates utilized the CHEST methodological guidelines with chronic wet or productive cough and Grading of Recommendations Assessment, Development, and Evaluation framework and also performed a systematic review addressing key questions concerning the management of childhood disease for children 14 years and younger.

Guidance provided by the expert panel focused on recommendations to answer six key questions concerning the management of children 14 years and younger with a chronic wet cough unrelated to established chronic lung disease. The recommendations are:

1. Chronic cough is defined as the presence of a cough 4 weeks or longer in duration.
2. Assessment of the effect of the cough on the child and the family be undertaken as part of clinical consultation.
3. Evaluation of a chronic cough should be done with a systematic approach with pediatric-specific cough management protocols or algorithms.
4. Chest radiograph and, when age appropriate, spirometry with bronchodilator be undertaken as evaluation; tests for pertussis infection only to be performed if clinically suspected.
5. Chronic wet cough with no specific clinical features should receive antibiotics for 2 weeks targeted for common respiratory bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).
6. When cough persists despite 2 weeks of appropriate antibiotics, it is recommended to continue for an additional 2 weeks.
7. Additional tests (eg skin prick test, Mantoux, bronchoscopy, chest CT scan) should be individualized in accordance with the clinical setting and child's clinical symptoms and signs.

The panel recognizes the need for prospective studies to assess current

algorithms outcomes of children with chronic cough. Both articles can be found on the guidelines section of the CHEST site.

John Bishara, DO
Fellow-in-Training Member

Pulmonary Physiology, Function, and Rehabilitation

Functional imaging of the lung

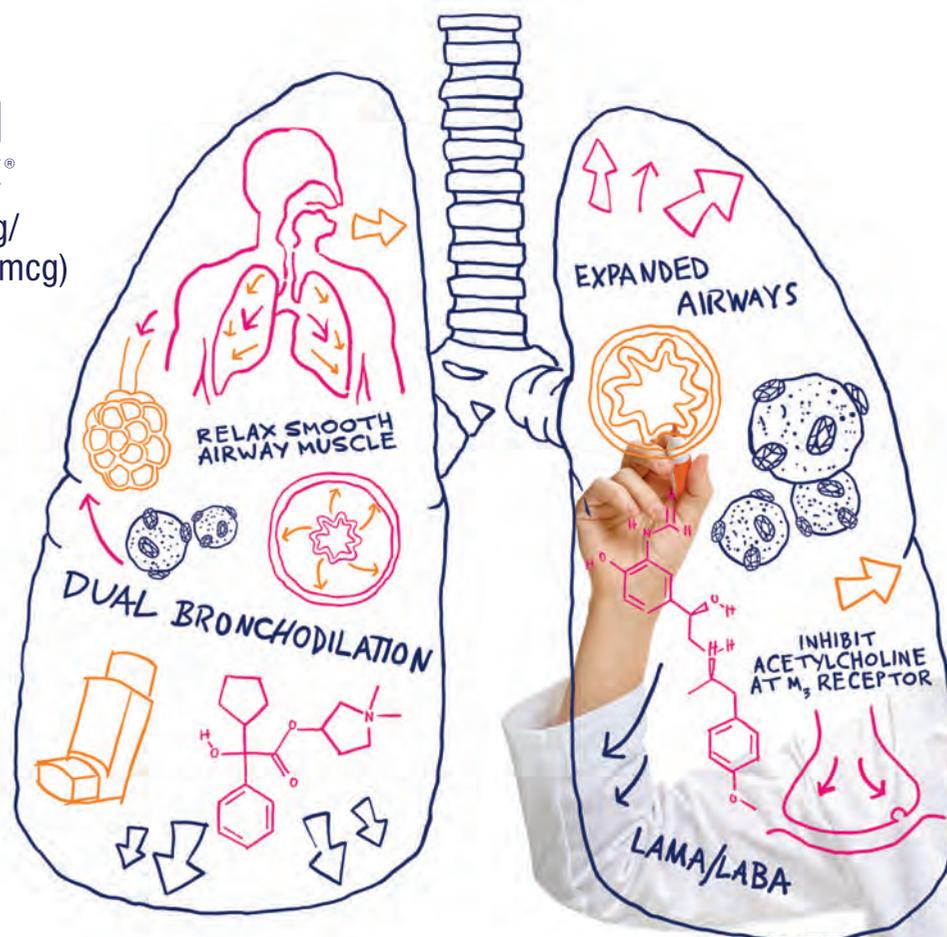
Quantifying heterogeneity of ventilation and gas exchange in lung diseases remains a clinical challenge. Conventional pulmonary function test is insensitive to regional changes. The multiple inert gas elimination technique can quantify ventilation-perfusion distribution, but it requires invasive instrumentation (eg, pulmonary artery catheterization) and is not practical for clinical use. Computed tomography (CT) scans delineate spatial changes in lung structures but do not directly measure changes in ventilation and gas exchange. With its radiation, it is difficult to apply CT scanning repeatedly in patients. More recently, MR imaging techniques have been developed to directly "visualize" and quantify regional lung function (Kruger SJ, et al. *J Magn Reson Imaging*. 2016;43(2):295; Roos JE, et al. *Magn Reson Imaging Clin N Am*. 2015;23(2):217). These techniques employ inhalation of gases, such as oxygen, perfluorinated gases, and hyperpolarized ^3He and ^{129}Xe . Hyperpolarized ^3He has been studied the most; however, the dwindling supply of ^3He gas and its rising cost have prevented its further development. ^{129}Xe has abundant supply and has emerged to be the inert gas of choice for MR imaging. Hyperpolarized ^{129}Xe can measure ventilation, like hyperpolarized ^3He . In addition, Xe diffuses into alveolar barrier (interstitium and plasma) and red blood cells, where it exhibits distinct resonant frequency shifts that can be captured by MR. Therefore, in one test, information on pulmonary ventilation and gas transfer can be obtained. To date, the results from MR imaging studies have provided new insights into the pathophysiology of obstructive

Continued on page 68



BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting beta₂-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

CONTRAINDICATION: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with a hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition

- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting beta₂-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines

- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI ($\geq 2\%$ and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non-potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta₂-agonists

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

INTELLIGENT FORMULATION*

Intelligent formulation for a pMDI using patented CO-SUSPENSION™ Delivery Technology¹

MAXIMIZE BRONCHODILATION†

Improved lung function[‡] vs placebo including¹

- 150-mL improvement in predose FEV₁ at 24 weeks
- Nearly a 300-mL improvement in peak FEV₁ at 24 weeks
- Nearly a 200-mL improvement in FEV₁ at 5 minutes on Day 1

In a separate study vs placebo

- Achieved a 381-mL improvement in peak inspiratory capacity on Day 29^{§||}

Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.¹

BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.

* BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.¹

† Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).^{1,3}

§ Results from a separate Phase IIIb trial (n=35). There was a significant mean improvement in primary endpoint FEV₁ AUC₀₋₂₄ on Day 29 vs placebo.^{2||} Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint.[#] Similar results seen in a second Phase IIIb trial (n=75).^{2||}

LEARN MORE AT
DUALBRONCHODILATION.COM

- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting beta₂-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

LIMITATION OF USE: Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

‡ Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV₁ of <80% of predicted normal values, and FEV₁/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV₁ at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; P<0.0001 for all treatment comparisons.^{1,3} Statistically significant results were also seen in Trial 2.^{1,3}

|| Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI AEROSPHERE compared with placebo in subjects with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Inclusion criteria were consistent with the two 24-week pivotal trials. Adverse events were numerically similar across treatment arms.²

[¶] Primary endpoint, FEV₁ AUC₀₋₂₄; Study A – BEVESPI AEROSPHERE (n=35) vs placebo (n=31) = 249 mL (baseline FEV₁ 1.382 L and 1.345 L, respectively); Study B – BEVESPI AEROSPHERE (n=65) vs placebo (n=65) = 265 mL (baseline FEV₁ 1.328 L and 1.333 L, respectively); both P<0.0001.²

[#] Secondary endpoint, Peak IC (evening): Study A – BEVESPI AEROSPHERE (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI AEROSPHERE (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both P<0.0001.²

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. 2. Data on File, 3270300, AZPLP. 3. Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357.

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BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. [see Warnings and Precautions (5.1) in the full Prescribing Information]

INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma [see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information].

DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions (5.1) in the full Prescribing Information]. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product [see Warnings and Precautions (5.5) in the full Prescribing Information].

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective, or the patient needs more inhalations of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled medicines containing beta₂-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason [see Drug Interactions (7.1) in the full Prescribing Information].

Paradoxical Bronchospasm

As with other inhaled medicines, BEVESPI AEROSPHERE can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BEVESPI AEROSPHERE, it should be treated immediately with an inhaled, short-acting bronchodilator. BEVESPI AEROSPHERE should be discontinued immediately, and alternative therapy should be instituted.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms [see Clinical Pharmacology (12.2) in the full Prescribing Information]. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta₂-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see Clinical Pharmacology (12.2) in the full Prescribing Information]. The decrease in serum potassium is usually transient, not requiring supplementation. Beta₂-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of Urinary Retention

BEVESPI AEROSPHERE should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma [see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information].

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Hypersensitivity reactions [see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]
- Cardiovascular effects [see Warnings and Precautions (5.6) in the full Prescribing Information]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.9) in the full Prescribing Information]
- Worsening of urinary retention [see Warnings and Precautions (5.10) in the full Prescribing Information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV₁) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

Additional Adverse Reactions: Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated [see *Warnings and Precautions (5.3) in the full Prescribing Information*].

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta₂ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta₂-agonists, especially when the recommended dose of the beta₂-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta₂-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of BEVESPI AEROSPHERE with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions (5.9, 5.10) and Adverse Reactions (6) in the full Prescribing Information*].

USE IN SPECIFIC POPULATIONS**Pregnancy****Teratogenic Effects:**

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BEVESPI AEROSPHERE.

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m² basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m² basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m² basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m² basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m² basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m² basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m² basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because beta₂-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

Pediatric Use

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

Geriatric Use

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤ 30 mL/min/1.73 m²) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

OVERDOSAGE

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

Glycopyrrolate

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta₂-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

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Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: Aventis Pharma LTD, Holmes Chapel CW48BE, United Kingdom

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Continued from page 63

and restrictive lung diseases. With continuous development, MR imaging of the lung could become a clinically useful tool in the near future.

Yuh-Chin T. Huang, MD, MHS,
FCCP
Steering Committee Member

Thoracic Oncology

Immune-mediated pneumonitis and PD-1 inhibition

Inhibitors of the programmed cell death 1 receptor (PD-1) have shown significant promise in the treatment of advanced stage malignancy. With the recent expan-

sion of indications for use of these agents, the number of patients treated will continue to grow. Clinicians must be aware of their potential for serious adverse side effects, including dermatitis, colitis, and potentially life-threatening pneumonitis.

The development of pneumoni-

tis secondary to PD-1 inhibitions is reported to occur in 2% to 5% of patients and can present at any time during therapy, with 1% of patients developing grade 3 or higher pneumonitis.^{1,2} The most common symptoms are dyspnea and cough, though one-third

Continued on page 71

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SATURDAY OCTOBER 28

2:00 PM - 4:00 PM (Open Invitation)

Lung Health Experience—Community COPD Screening

Nathan Phillips Square

100 Queen St W, Toronto, ON M5H 2N2, Canada

SUNDAY OCTOBER 29

9:00 AM - 5:00 PM

Donor Lounge

Convention Center, 803B

3:15 PM - 4:15 PM

Foundation Session: Severe Asthma

Care at Its Best: Shared Decision Making"

Convention Center, 716A

4:30 PM - 5:30 PM

Foundation Session: No Money, No Mission: Tips for Getting Your Grant Funded

Convention Center, 716B

MONDAY OCTOBER 30

9:00 AM - 5:00 PM

Donor Lounge

Convention Center, 803B

8:45 AM - 10:00 AM

Opening Session / CHEST Foundation Awards Convocation

Convention Center, Hall G, Level 800

6:30 PM - 8:00 PM

Boehringer Ingelheim and CHEST

Foundation Patient Engagement Summit

Sheraton, Grand Ballroom Centre

8:00 PM - 10:00 PM

Young Professionals Reception

(RSVP chestfoundation.org/youngprofessionals)

The Fifth Social Club

225 Richmond St W Suite 100

Toronto, ON M5V 1W2, Canada

TUESDAY OCTOBER 31

9:00 AM - 5:00 PM

Donor Lounge

Convention Center, 803B

WEDNESDAY NOVEMBER 1

9:00 AM - 12:00 PM

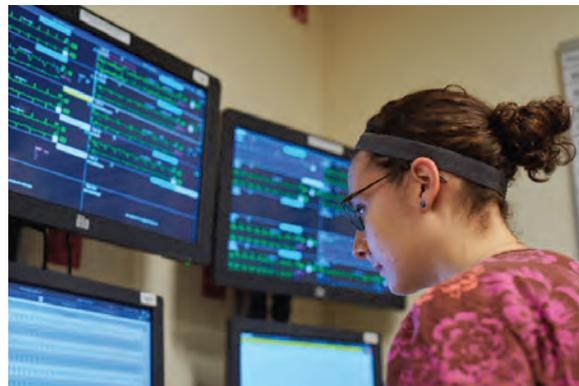
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of patients are asymptomatic at presentation.² Radiographic and pathologic features vary greatly and include organizing pneumonia, interstitial pneumonitis, hypersensitivity pneumonitis, or diffuse alveolar damage.³

While pneumonitis due to PD-1 inhibition is reportedly uncommon, the increasing number of patients expected to receive these medications will predictably result in increasing overall frequency of pneumonitis cases. In addition, the lack of large prospective randomized trials and reliance on radiographic rather than pathologic data in diagnosing immune-mediated pneumonitis gives one pause. Given the variability of presentation, lack of routine pathologic data, and increasing use of dual agents (eg, PD-1 and CTLA-4), chest physicians and medical oncologists should have a high index of suspicion yet practice equipoise in patients receiving immunotherapy who develop unexplained pulmonary symptoms or infiltrates. More research is needed to help improve the multidisciplinary diagnosis and treatment of this potentially serious complication.

David Maurice Chambers, MD
 Fellow-in-Training Member
 Jason Atticus Akulian, MD, MPH
 Steering Committee Member

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Pulmonary Vascular Disease

Pulmonary Arterial Hypertension Associated With SLE

While pulmonary arterial hypertension (PAH) commonly complicates scleroderma (SSc), it is a rare complication of other connective tissue diseases (CTD), such as systemic lupus erythematosus (SLE). In the few prospective studies that utilize right-sided heart catheterization (RHC), the estimated prevalence of PAH in SLE is about 4%. However, since the prevalence of SLE is 10 to 15 times greater than SSc in the United States, the true prevalence of SLE-PAH may be higher than previously thought, and, thus, clinically relevant. Despite this, little is known about SLE-PAH.

A recent retrospective study from the French Pulmonary Hypertension Registry has added significantly to our understanding of this complication of SLE. Hachulla and colleagues studied 51 patients with RHC-proven SLE-PAH compared with 101 SLE control subjects without PAH. While the authors did not find any relevant differences in the demographics between groups, they did find a significantly higher prevalence of SSA and SSB antibodies in SLE-PAH. Interestingly, the presence of anti-U1 RNP antibody appeared to be less common in SLE-PAH patients; this lack of association is in contrast to prior studies in mixed CTD patients with anti-U1 RNP antibodies in which the prevalence of PAH can be as high as 60%. Further, none of the SLE-PAH patients demonstrated an acute response to vasodilator challenge during RHC, emphasizing that this maneuver does not need to be performed in SLE patients at risk of PAH. Trends toward improved survival in SLE-PAH patients treated with hydroxychloroquine are preliminary and hypothesis-generat-

ing but require confirmation in larger clinical studies.

Stephen Mathai, MD, FCCP
 Chair
 Leena Palwar, MD
 Fellow-in-Training Member

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This Month in CHEST

Editor's Picks



BY RICHARD S. IRWIN, MD,
 MASTER FCCP
 Editor in Chief, CHEST

A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults.

By Dr. M. W. Semler, et al.

Sleep Apnea and Hypertension: Are There Sex Differences? The Vitoria Sleep Cohort.

By Dr. I. Cano-Pumarega, et al.



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¹ Tapson, et al. "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

² Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

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⁴ Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

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