

CHEST[®] Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY DR. MIKE NELSON

Dr. Michael E. Nelson, FCCP, advises taking the reprieve as an opportunity to become familiar with the MIPS requirements.

MACRA flexibility is a win for most practices

BY GREGORY TWACHTMAN
Frontline Medical News

Federal flexibility in compliance with the first year of MACRA reforms is being perceived as a win for most physicians. Pressure from a number of physician organizations is credited in part for the Centers for Medicare & Medicaid Services' decision to reduce some of the reporting requirements for 2017 that will affect compensation in 2019.

Michael E. Nelson, MD, FCCP, who practices pulmonary, critical care and sleep medicine in Shawnee Mission, Kansas, said he suspects

the change will be good news for most physicians participating in the Merit-Based Incentive Payment System (MIPS), but that "the devil will be in the details."

Hopefully, even the most unprepared of physicians will be able to avoid a reimbursement reduction by providing some QPP (Quality Payment Program) data," he said.

"Independent of whether Obamacare is supplanted by HillaryHealth or DonaldDocs, pun intended, the QPP program will continue until such time as a new mandate is received from Congress. So, unless you have MACRAphobia require-

See **MACRA** • page 20

Post-hoc analyses strengthen FLAME's findings

LAMA/LABA benefited all subgroups

BY TED BOSWORTH
Frontline Medical News

LONDON – In chronic obstructive pulmonary disease (COPD), the advantage of a long-acting beta agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) over a LABA plus an inhaled corticosteroid (ICS) was observed in every subgroup in the FLAME trial evaluated, according to post hoc analyses presented at the annual congress of the European Respiratory Society.

"We thought that we might not see the difference in the COPD patients with more severe disease, but the

advantage was consistent even among those who entered the trial on triple therapy," reported Jadwiga A. Wedzicha, MD, professor of respiratory medicine at the National Heart and Lung Institute, Imperial College, London.

FLAME, the recently published study that compared LABA/LAMA to LABA/ICS, was planned as a non-inferiority study with the underlying hypothesis that LABA/LAMA would perform as well as LABA/ICS for the primary outcome of annual rate of COPD exacerbations (N Engl J Med. 2016;374:2222-34). Instead,

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Macrolide okay in GOLD 1, 2

BY SARA FREEMAN
Frontline Medical News

LONDON – Maintenance azithromycin may be best reserved for patients with mild to moderate chronic obstructive pulmonary disease (COPD) who also have few symptoms, based on an analysis of the COLUMBUS randomized controlled trial.

Significantly fewer exacerbations (1.06 vs. 2.62; $P = .02$) occurred at 1 year in patients treated with the macrolide antibiotic rather than placebo if they were classified as having GOLD [Global Initiative for Chronic Obstructive Lung Disease] stage 1 or 2 versus stage 4.

Study participants who were classified as being part

of GOLD group C (which includes patients with a high risk of COPD exacerbation but a low level of COPD symptoms) who were treated with maintenance azithromycin were also more likely to have fewer exacerbations at 1 year, compared with patients classified as being part of GOLD group

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Reduce lung function
decline with Esbriet¹⁻⁴



DEMONSTRATED EFFICACY*

- Esbriet had a significant impact on lung function vs placebo in ASCEND^{2,3}
 - 48% relative reduction in risk of a meaningful decline in lung function ($\geq 10\%$ decline in %FVC) at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference; $P < 0.001$)**
 - 2.3x as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference; $P < 0.001$)**
- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND^{2,3}**
- **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}**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)²



ESTABLISHED MANAGEMENT PLAN

- The recommended daily dosage is 3 capsules, 3 times a day (2403 mg/day) with food, titrated to full dosage over a 14-day period²
- Flexible dosing for appropriate modification to help manage potential adverse reactions (patients may require dose reduction, interruption, or discontinuation)²
 - eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash



COMMITTED TO PATIENTS

- Esbriet Access Solutions offers a full range of access and reimbursement support for your patients and practice
- The Esbriet Inspiration ProgramTM motivates patients to stay on treatment with information and encouragement
- Clinical Coordinators are available to provide education to patients with IPF through in-office programs



WORLDWIDE PATIENT EXPERIENCE

- Esbriet has been approved outside the US since 2011¹
- More than 27,000 patients have taken pirfenidone worldwide¹

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. Rarely 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.

ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity. *The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and %DL_{co} (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC $\geq 50\%$ and %DL_{co} $\geq 35\%$. The primary endpoint was change in %FVC from baseline to week 72.

[†]Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

Genentech

A Member of the Roche Group

**Recommended by the ATS/ERS/JRS/ALAT
Clinical Practice Guideline for the treatment of IPF.**

Conditional recommendation, moderate confidence in estimates of effect.⁵¹

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

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 Esbriet 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 (≥10%) were 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 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 disease 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. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **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. **5.** Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline [published correction appears in *Am J Respir Crit Care Med*. 2015;192(5):644]. *Am J Respir Crit Care Med*. 2015;192(2):e3-e19.

Esbriet[®]
(pirfenidone) capsules 267mg

Characteristics predict response

Azithromycin from page 1

D (which includes patients with a high risk of COPD exacerbation and a high level of COPD symptoms), who took the same antibiotic (0.45 vs. 2.18; P less than .01).

A high serum eosinophil level (2% or higher) was a third factor found in COPD patients that was predictive of fewer exacerbations following azithromycin use (1.26 vs. 2.5; $P = .02$).

“Azithromycin maintenance therapy should not be given to every COPD patient,” Remco Djamin, MD, of Amphia Hospital Breda in the Netherlands said in an interview at the annual congress of the European Respiratory Society. There is, of course, the concern over antibiotic resistance developing and macrolide

antibiotic use has been linked with heart problems such as arrhythmia.

These data show, however, that there are certain predictors that might help clinicians decide if long-term antibiotic therapy might be beneficial for their patients who are experiencing frequent acute exacerbations of COPD.

Esbriet
(pirfenidone) capsules 267mg

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. Rarely 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)*]

ESBRIET® (pirfenidone)

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 (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 1.

Table 1. 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 postapproval 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

Further research should look at the dosing and duration of azithromycin, Dr. Djamin suggested. Perhaps reducing the dose by half to 250 mg three times per week would be just as good; maybe 6 months' rather than 12 months' treatment would be sufficient, or perhaps it could be given intermittently. The aim is to

ensure that patients are not being exposed unnecessarily, as there is concern over antibiotic resistance.

The use of azithromycin is not currently recommended in guidelines for COPD management to prevent exacerbations, but it is something that is likely to be added to the guidelines, as the evidence for its benefit

mounts, Dr. Djamin said.

In addition to COLUMBUS, there have been at least two other studies looking at long-term antibiotic use to prevent exacerbations in patients with COPD.

One (Am J Respir Crit Care Med. 2008;178:1139-47) showed erythromycin could decrease the exacerba-

tion rate at 1 year by 36%, compared with placebo, while the other (N Engl J Med. 2011;365:689-8) again showed a benefit for azithromycin, with a 27% decrease in the 1-year exacerbation rate.

In COLUMBUS, 92 patients who had experienced at least three or more acute COPD exacerbations in the previous year were randomized to treatment with azithromycin 500 mg or placebo, taken three times per week for 12 months.

This was a single-center, double-blind trial conducted in the Netherlands that showed a 42% reduction in the 1-year exacerbation rate could be achieved with the antibiotic treatment (Lancet Respir Med. 2014;2:361-8).

An additional benefit to using the antibiotic was seen in patients with GOLD stage 1-2 over patients with GOLD stage 4 and in patients with a higher percentage of serum eosinophils.

The GOLD stage 1-2 patients experienced fewer exacerbations leading to hospitalization, compared with patients with GOLD stage 4 (0.31 vs. 1.00; $P = .04$), while the patients with higher levels of eosinophils experienced fewer exacerbations requiring hospitalization than those patients with lower percentages of eosinophils (0.26 vs. 1.07; $P = 0.01$).

"[These patients'] exacerbations are often already being treated with antibiotics and so maintaining treatment has become one possible way of perhaps preventing exacerbations in the future," Dr. Djamin said, at the conference.

The study received no industry funding. Dr. Djamin had no competing interests to disclose.

ESBRIET® (pirfenidone)

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 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

Teratogenic Effects: **Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal doses up to 1000 and 300 mg/kg/day, 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, 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 dose of 1000 mg/kg/day).

8.3 Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

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.

ESBRIET® (pirfenidone)

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 2.2 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 overdose. 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 overdose, 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.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP,

comments: This study adds to the data supporting the use of thrice weekly macrolide in the prevention of COPD exacerbations in patients with frequent exacerbations. Importantly, it provides some guidance on which patients may benefit the most, given the concern for potential cardiac and antibiotic resistance complications. As suggested in the article, further study is needed to define the best treatment population and dosing strategy – especially since much of the effect of macrolide administration in chronic pulmonary diseases likely is immunomodulatory rather than one of pure antibiosis.

Asthma-COPD Overlap Syndrome definition under fire

BY TED BOSWORTH
Frontline Medical News

LONDON – A study comparing patient data with six definitions of the Asthma-COPD Overlap Syndrome (ACOS) found only one of the patients analyzed met all definitions. This provoked an animated discussion at the annual congress of the European Respiratory Society about the utility of ACOS as a clinical entity.

Of 864 patients diagnosed with COPD or asthma drawn from the Netherlands Epidemiology of Obesity cohort (a population-based study with 5,784 patients), 39.1% (338 patients) met at least one of the definitions of ACOS, while 0.1% (one patient) met the criteria for all six definitions.

When this finding was presented, the ERS audience first laughed and then applauded.

At the end of the presentation, long lines formed at the microphones. Every comment made was hostile to the concept of ACOS.

“Let us bring ACOS to an honorable death,” said one audience member. His point, reiterated by all who commented subsequently, was that ACOS confuses efforts to treat the underlying respiratory symptoms. Even in those who have both asthma and COPD, the speaker, like other members of the audience, said he considered the diagnosis of ACOS unhelpful.

The six definitions in the study included the latest and just published consensus definition from the ERS (Eur Respir J. 2016;48[3]:664-73).

According to the ERS definition, the key features of ACOS are age greater than 40 years, long-term history of asthma (since childhood or early adulthood), and significant exposure to cigarette or biomass smoke.

The other definitions analyzed included a medical history of both asthma and COPD, a self-reported history of both asthma and COPD, and a record of the proportion of a person’s vital capacity that he/she is able to expire in 1 second of forced expiration of less than 0.7 plus a record of fractionated nitric oxide concentration in exhaled breath of greater than or equal to 45 parts per billion.

Although attempted, a Venn diagram that would show overlapping subsets of patients that fell into these definitions “was not possible,” according to Tobias Bonten, MD, University of Leiden, the Netherlands.

Asthma duration was just over 10 years in those identified as having ACOS by medical history alone (registry-based definitions), just over 20 years in those with a medical history and objective evidence of impaired lung function, but about 40 years in those with a self-report of both asthma and COPD.

One area that all groups created by the ACOS definitions did have in common was demographic variables, such as median age, proportion of patients defined as overweight or obese by body mass index, and proportion who were current smokers.

Members of the audience acknowledged the importance of considering the coexistence of asthma and COPD, but expressed skepticism about the value of ACOS as a separate entity in the clinic.

“ACOS is something like the emperor’s new clothes,” one audience member said during the discussion. “It is important to identify asthma patients with obstruction because they have reduced lung function that should be treated more actively, but I find the definition [of ACOS] unnecessary,” he said.

A similar conclusion was drawn in a review article devoted to ACOS published last year (N Engl J Med. 2015;373[13]:1241-9). “It is premature to recommend the designation of ACOS as a disease entity,” the authors wrote.

This is a position widely shared by clinicians, judging from audience comments provoked by this demonstration.

For the sake of time, the moderators were forced to end the discussion with significant lines of clinicians at the microphone.

“It is quite clear that ACOS should die,” said one of the last speakers given a chance to voice an opinion. He suggested that the coexistence of asthma and COPD is something that “quite clearly can happen,” but he objected to definitions he said are unhelpful for clinical care.

Dr. Bonten reported no relevant financial relationships.

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

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Fluticasone furoate/vilanterol beats usual COPD care

BY AMY KARON
Frontline Medical News

A once-daily inhaled combination of fluticasone furoate and vilanterol was associated with an 8% lower rate of exacerbations in chronic obstructive pulmonary disease (COPD) than was usual care, with no increase in adverse effects, according to a multicenter trial designed to reflect real-world practice.

“Future effectiveness studies [like this one] are likely to influence clinical guidelines, not only for COPD but [also] for many other chronic diseases,” said Jørgen Vestbo, MD, of University Hospital of South Manchester NHS Foundation Trust, Manchester, England, and his associates, for the Salford Lung Study investigators. The findings were presented at the annual congress of the European Respiratory Society and published simultaneously in the *New England*

Journal of Medicine.

Current COPD guidelines are based on clinical trials of carefully selected and monitored patients, which substantially limits their usefulness in everyday practice, the researchers said. To help address that problem, their 12-month, prospective, open-label, parallel-group, randomized study enrolled 2,799 COPD patients in 75 general practices within a single urban area in the United Kingdom. Patients received 100 mcg of fluticasone furoate and 25 mcg of vilanterol or usual care. The primary outcome was the rate of moderate or severe exacerbations among patients who had experienced an exacerbation within 1 year before enrollment. Patients received all treatment from their usual providers and were monitored remotely for safety through electronic health records (*N Engl J Med*. 2016 Sep 4. doi: 10.1056/NEJMoa1608033).

Fluticasone furoate/vilanterol was associated with 1.74 moderate or severe exacerbations per year, compared with 1.9 events per year with usual-care group, for a statistically

“Future effectiveness studies [like this one] are likely to influence clinical guidelines, not only for COPD but [also] for many other chronic diseases,” said Dr. Vestbo and his associates.

significant difference of 8.4% (95% confidence interval, 1.1%-15.2%; $P = .02$). The trial arms had similar rates of COPD-related health care visits and first moderate or severe exacerbations. They also did not notably differ in terms of serious adverse

events of special interest, such as cardiovascular events (which affected 8% of patients in each group) or pneumonia (which affected 7% of fluticasone furoate/vilanterol patients and 6% of usual-care patients). Thirteen patients in each group developed fatal pneumonia, of which one case was considered related to usual care. The only other treatment-related death involved a deep-vein thrombosis and a pulmonary embolism in a patient receiving fluticasone furoate/vilanterol.

Medication switches were about twice as common (22%) in the intervention group than in the usual care group (11%), perhaps because of the open-label nature of the trial, the researchers said. Only 4% of patients receiving fluticasone furoate/vilanterol needed better disease control, half the rate of the usual care group.

Dr. Vestbo reported personal fees from study funder GlaxoSmithKline.

All subgroups benefited

FLAME from page 1

the 11% lower rate of exacerbations for LABA/LAMA proved statistically significant ($P = .003$).

Six post hoc FLAME analyses were presented at the 2016 ERS Congress to further explore this result. All supported the main result. In addition to evaluating those who entered the trial on a LABA/LAMA/ICS triple-therapy combination, the analyses covered a broad array of subgroups defined by age, smoking history, and COPD severity as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications.

In FLAME, 3,362 COPD patients who had at least one exacerbation in the preceding year were randomized to the LABA indacaterol (110 mcg) plus the LAMA glycopyrronium (50 mcg) once daily or the combination of the LABA salmeterol (50 mcg) and the ICS fluticasone (500 mcg) twice daily. In addition to the relative advantage on the primary outcome of any exacerbation, the LABA/LAMA combination also significantly reduced the rate of moderate to severe exacerbations (P less than .001), and it extended the times to the first moderate to severe exacerbation (P less than .001) and the first severe exacerbation ($P = .046$), according to the published data.

In the post hoc analyses, the advantage of LABA/LAMA relative to LAMA/ICS was remarkably consis-

tent. For example, in stratifications made for age (less than 55 years, 55 to less than 65 years, 65-75 years, and greater than or equal to 75 years) at least a numerical advantage of LABA/LAMA was seen in all age groups for prevention of any exacerbation, and the difference reached statistical significance for those in the age group 55 to greater than 65 years. For prevention of moderate to

We thought that we might not see the difference in the COPD patients with more severe disease. The advantage of LABA/LAMA relative to LAMA/ICS was consistent even among those who entered the trial on triple therapy, said Dr. Wedzicha.

severe exacerbations, the treatments were found to be equivalent for individuals younger than 55 years, but LABA/LAMA was statistically superior for the other three age categories.

For ex-smokers, unlike current smokers, the numerical advantage of LABA/LAMA over LABA/ICS for reduction in the rate ratio of all exacerbations did not reach statistical significance, but the LABA/LAMA combination did provide a statistically significant advantage for both

ex-smokers and current smokers for moderate to severe exacerbations.

For patients with two or more exacerbations in the year prior to enrollment in FLAME, the relative degree of protection was of magnitude similar to that of patients with only one exacerbation even though the relative advantage in those with multiple prior exacerbations did not reach statistical significance. However, the lack of significance was likely due to the relatively small number of patients in this subpopulation, according to Dr. Wedzicha.

Similarly, the LABA/LAMA combination was at least numerically superior to LABA/ICS for all exacerbations and for moderate to severe exacerbations across GOLD classifications with one exception. When compared for relative protection against moderate to severe exacerbations, there was a slight and non-significant disadvantage for LABA/LAMA, but, again, Dr. Wedzicha reported, “the number of patients in this subgroup was quite small.”

In another FLAME post hoc analysis, the odds ratio (OR) for exacerbations among the 1,893 patients (56.3%) who were on ICS at study entry was found to be almost identical to the OR among those who were not. Specifically, the ORs for all exacerbations and moderate to severe exacerbations were 0.88 ($P = .008$) and 0.86 ($P = .018$), respectively, for those previously treated with ICS and 0.88 ($P = .021$) and 0.78 ($P = .002$), respectively, for those who had not

been treated with ICS.

The LABA/LAMA combination was also superior to LABA/ICS for improvements in quality of life, which was measured via the St. George’s Respiratory Questionnaire. With an improvement of at least four units on the St. George’s Respiratory Questionnaire defined as clinically meaningful, 49.5% of LABA/LAMA patients versus 43.8% of LABA/ICS patients (P less than .024) benefited on this measure.

Overall, the results from the FLAME post hoc analyses have demonstrated “remarkable consistency,” and “imply that LABA/LAMA is the first choice of treatment for COPD patients at risk of exacerbation,” Dr. Wedzicha reported.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: These additional post-hoc analyses of the FLAME trial presented at the ERS conference are helpful in a descriptive nature, but aside from the conclusions drawn from the peer-reviewed publication, one needs to take caution when addressing what conclusions can be drawn from such an analysis.



PULMONARY PERSPECTIVES® The sun should never set on an “un-ultrasound-ed” pleural effusion

BY RICARDO FRANCO-SADUD, MD; AND NILAM J. SONI, MD, MS

The adage, “the sun should never set on an untapped pleural effusion,” was instilled in physicians for generations. However, anyone who practices medicine currently knows the sun often rises and sets several times before a pleural effusion is tapped. Why the change in mindset? Since the American Board of Internal Medicine removed the requirement for internal medicine residents to perform a minimum number of bedside procedures for certification, fewer graduating residents feel comfortable performing thoracentesis.

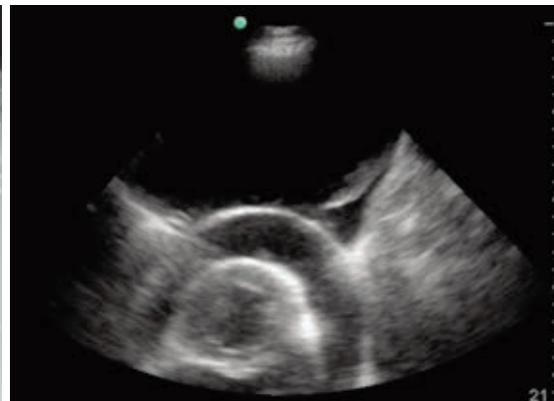
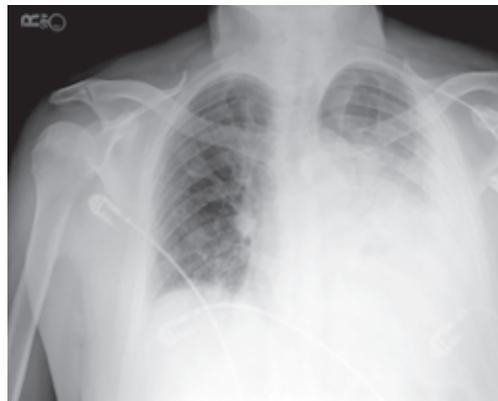
Additionally, the fear of litigation and institutional persecution from a postprocedure complication has caused many frontline clinicians to shy away from performing thoracentesis. Most important, we now appreciate that not all pleural effusions need to be tapped immediately, and the clinical decision making about the timing and technique to drain a pleural effusion is more complex than previously thought.

In recent years, the availability of portable ultrasound (US) for bedside diagnostics and procedural guidance has revolutionized the practice of medicine, including the management of pleural effusions. When confronted with an obscured lower lobe on chest radiograph, clinicians were previously relegated to primitive bedside maneuvers, such as percussion or auscultation, to make critical management decisions. Now, clinicians are able to look inside the body with point-of-care US and visually assess a pleural effusion before making any decisions. Point-of-care US has shifted the paradigm in the management of pleural effusions in several ways.

US allows rapid detection and differentiation of pleural effusions from other pathologic findings.

Chest radiographs cannot accurately differentiate a pleural effusion from other common conditions, such as pneumonia, atelectasis, or an elevated hemidiaphragm. US is the only bedside diagnostic modality that can rapidly differentiate these conditions within seconds and may reveal unsuspected findings, such as a mass or pericardial effusion.

For example, the pleural US exam of a patient confirmed the presence of a large, left-sided pleural effusion



An obscured lower lobe on chest radiograph necessitated percussion or auscultation to make management decisions. Point-of-care ultrasound allows visual assessment of a pleural effusion.

(Figure, right) but also revealed an unsuspected large pericardial effusion (See dot.) that was causing hemodynamic compromise. Thus, management of this patient shifted focus from the pleural effusion to the pericardial effusion, and urgent pericardiocentesis was performed. The sensitivity of US to detect a pleural effusion is proportional to the volume of fluid, reaching 100% with as little as 100 mL of fluid (Kalogairinou-Motogna et al. *Med Ultra*. 2010;12[1]:12). The diagnostic accuracy of US for detection of pleural effusions is comparable to CT scans of the chest and superior to portable chest radiographs (Lichtenstein et al. *Anesthesiology*. 2004;100[1]:9).

US characterizes pleural effusions to determine the most appropriate management strategy.

Any clinician with basic ultrasonography skills can learn to evaluate pleural effusions and categorize them as simple or complex based on the sonographic appearance. Visualization of fibrinous stranding or loculations increases the probability of pleural fluid being exudative and often drives the decision to drain the fluid. The density and distribution of loculations can guide decisions about the most appropriate type of drainage procedure – thoracentesis versus tube thoracostomy versus surgical intervention. Use of color flow Doppler US allows clinicians to assess whether or not pleural fluid is free flowing and amenable to drainage, potentially saving the patient from an unnecessary attempt at drainage. US affords frontline clinicians the ability to streamline consultation with the most appropriate specialist based on the type of drainage procedure indicated and potentially prevent duplicate procedures on the same patient from different specialists.

US reduces the risk of postprocedure complications from thoracentesis.

The risk of postthoracentesis pneumothorax was reported to be as high as 20%-39% before the routine use of point-of-care US (Grogan et al. *Arch Int Med*. 1990;150:873). US guidance has been shown to increase procedural success rates and decrease the risk of postprocedure pneumothorax (2.7%), cost of hospitalization, and length of stay (Mercaldi et al. *Chest*. 2015;143[2]:532). Regardless of the chest radiograph or CT scan findings, if the US exam reveals a scant volume of pleural fluid, or densely loculated pleural fluid, clinicians can avoid unnecessary attempts at bedside drainage, which likely partly accounts for the reduction in postprocedure pneumothorax. Use of US for needle site selection may prevent up to 10% of potential accidental organ punctures and increases accurate site selection by 26%, compared with chest radiograph and physical examination findings combined (Diacon et al. *Chest*. 2003;123:436).

US facilitates patient-centered care.

Point-of-care US is the only new technology that has taken clinicians back to the bedside to spend more time with patients. Clinicians can simultaneously perform an US exam and converse with patients to gather a medical history. The US image serves as a tool to help patients understand their condition and facilitates shared decision making with clinicians at the bedside.

As more specialties have gained expertise in thoracic ultrasonography, the use of US guidance for thoracentesis has evolved to become the stan-

dard of care in many hospitals in the United States. Besides pulmonary specialists, several acute care specialists, including hospitalists, intensivists, and emergency medicine physicians, are routinely using point-of-care US to guide diagnostic decision making and procedures. Over the past 10 years, nearly a dozen procedure services led by internal

medicine-trained hospitalists have been created at academic institutions that are routinely performing US-guided thoracenteses with low complication rates (Franco-Sadud et al. *SGIM Forum*. 2016;39[5]:13). More important, US is being used on the front lines to expeditiously evaluate pleural effusions and perform a diagnostic thoracentesis or consult with the appropriate subspecialist.

Even though demonstration of competency in bedside procedures is no longer required for board certification in internal medicine, many internal medicine residency programs have incorporated diagnostic and procedural point-of-care US training into their education curriculum (Schnobrich et al. *JGME*. 2013;5[3]:498). Further, approximately 62% of medical schools report integrating US education into their medical student curriculum, and in coming years, most medical students will likely graduate with a basic skill set in point-of-care ultrasonography (Bahner et al. *Academic Med*. 2014;89[12]:1681). As point-of-care US education becomes integrated in training of physicians and other health-care providers, use of US to guide management of pleural effusions could become universally practiced and accepted as the new standard of care. Thus, it is plausible that a day will come in the near future when the sun will not set on an “un-ultrasound-ed” pleural effusion.

Dr. Franco-Sadud is with the section of hospital medicine/division of general internal medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; Dr. Soni is with the section of hospital medicine and the section of pulmonary and critical care medicine, South Texas Veterans Health Care System and University of Texas Health Science Center, San Antonio.

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Important Safety Information

WARNING: ASTHMA-RELATED DEATH

- Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) 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.
- When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

CONTRAINDICATIONS

- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

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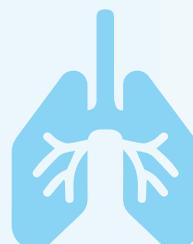
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Supporting Clinical Study Information

*In a randomized, double-blind (RDB) study of 1039 patients[‡] symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV₁ (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) ($P<0.001$).¹ (In an RDB, placebo-controlled study of 609 patients[‡] symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily [n=108] demonstrated a change from baseline in wm FEV₁ [0-24 hours] at the end of the 12-week treatment period vs FF 100 mcg once daily [n=106] of 116 mL [95% CI: -5, 236; $P=0.06$].²)

†In a 24- to 76-week RDB study of 2019 patients[‡] with ≥ 1 exacerbations in the prior year, BREO 100/25 once daily (n=1009) reduced the risk of experiencing an exacerbation by 20% (hazard ratio=0.795, $P=0.036$) vs FF 100 mcg once daily (n=1010).³ An exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥ 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

[‡]Studies included patients with asthma ≥ 12 years of age; BREO is only approved for use in patients ≥ 18 years of age.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines 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 BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- 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. Taper patients slowly from systemic corticosteroids if transferring to BREO.

WARNINGS AND PRECAUTIONS (cont'd)

- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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.

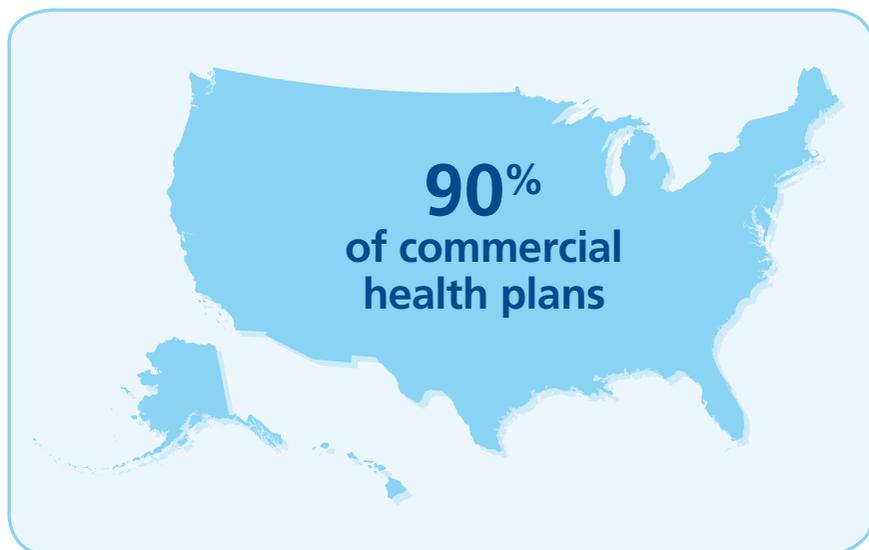


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SOURCE: Managed Markets Insight & Technology, LLC, database as of August 2016.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- 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.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS

- In a 12-week trial, adverse reactions ($\geq 2\%$ incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions ($\geq 2\%$ incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions ($\geq 2\%$ incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO on the following pages.

References: 1. Bernstein DI et al. *J Asthma*. 2015;52(10):1073-1083. 2. Bleecker ER et al. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561. 3. Bateman ED et al. *Thorax*. 2014;69(4):312-319.

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For local formulary information about BREO,
please contact your GSK sales professional.

What you need to know about this formulary information:

[§]Covered without restriction means reimbursement from a health plan with no accompanying step edits or prior authorizations.

Formulary status may vary and is subject to change. Formulary coverage does not imply clinical efficacy or safety. Benefits designs offered by plans may vary. Actual benefits and out-of-pocket costs are determined by each plan administrator in accordance with its respective policy and procedures. Consumers may be responsible for some out-of-pocket costs based on an individual's plan.

The information provided is not a guarantee of coverage or payment (partial or full). Please verify coverage with and obtain most current information from plan sponsors. GSK does not endorse individual plans.

ADVERSE REACTIONS (cont'd)

- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- BREO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non-potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.

USE IN SPECIFIC POPULATIONS

- BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

BREO[®] ELLIPTA[®]
(fluticasone furoate 100 mcg and
vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation
BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the asthma indication. See full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, 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 LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) 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, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

1.2 Treatment of Asthma BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, 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), Adverse Reactions (6.2), Use in Specific Populations (8.4)]. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS. **Important Limitation of Use:** BREO is NOT indicated for the relief of acute bronchospasm.

4 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions: Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required [see Warnings and Precautions (5.2)]; Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients [see Warnings and Precautions (5.11), Description (11) of full prescribing information].

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS 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, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

A 28-week, placebo-controlled, US trial that compared 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; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted.

5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO 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 reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO 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 treatment with BREO, 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 to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta₂-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines 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 BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Local Effects of ICS In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO continues, but at times therapy with BREO 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.

5.6 Immunosuppression Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox 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 affect 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 a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is 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 chickenpox develops, treatment with antiviral agents may be considered. ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.7 Transferring Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. 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 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 BREO may control COPD or 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, a severe COPD exacerbation, 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, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV₁ or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, 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 BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, 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.

5.8 Hypercorticism and Adrenal Suppression Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)]. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO 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 who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole or other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information].

5.10 Paradoxical Bronchospasm As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.

5.11 Hypersensitivity Reactions, Including Anaphylaxis Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO [see Contraindications (4)].

5.12 Cardiovascular Effects Vilanterol, 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, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO 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. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. 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, 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.

5.14 Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of ICS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.15 Coexisting Conditions BREO, like all medicines 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 ketacidosis.

5.16 Hypokalemia and Hyperglycemia Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In clinical trials evaluating BREO in subjects with COPD or asthma, there was no evidence of a treatment effect on serum glucose or potassium.

5.17 Effect on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. [See Use in Specific Populations (8.4) of full prescribing information.]

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS 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 trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. [See Warnings and Precautions (5.1).] Systemic and local corticosteroid use may result in the following: *Candida albicans* infection [see Warnings and Precautions (5.4)]; Immunosuppression [see Warnings and Precautions (5.6)]; Hypercorticism and adrenal suppression [see Warnings and Precautions (5.8)]; Reduction in bone mineral density [see Warnings and Precautions (5.13)]. 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.

6.2 Clinical Trials Experience in Asthma BREO for the treatment of asthma was studied in 18 double-blind, parallel-group, controlled trials (11 with placebo) of 4 to 76 weeks' duration, which enrolled 9,969 subjects with asthma. BREO 100/25 was studied in 2,369 subjects and BREO 200/25 was studied in 956 subjects. While subjects aged 12 to 17 years were included in these trials, BREO is not approved for use in this age-group [see Use in Specific Populations (8.4)]. The safety data described below are based on two 12-week efficacy trials, one 24-week efficacy trial, and two long-term trials.

12-Week Trials Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years.

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.

Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years.

In Trial 2, adverse reactions ($\geq 2\%$ incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346] or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).

24-Week Trial Trial 3 was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.

12-Month Trial Long-term safety data is based on a 12-month trial that evaluated the safety of BREO 100/25 once daily (n = 201), BREO 200/25 once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown for Trials 1 and 2 above, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO 100/25 or BREO 200/25 for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

Exacerbation Trial In a 24- to 76-week trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010) (Trial 5). Subjects participating in this trial had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO is not approved for use in this age-group [see Use in Specific Populations (8.4)]. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 (n = 151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

6.3 Postmarketing Experience In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. 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 BREO or a combination of these factors.

Cardiac Disorders Palpitations, tachycardia.

Immune System Disorders Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

Musculoskeletal and Connective Tissue Disorders Muscle spasms.

Nervous System Disorders Tremor.

Psychiatric Disorders Nervousness.

Respiratory, Thoracic, and Mediastinal Disorders Paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4 Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) [see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information].

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants Vilanterol, like other β_2 -agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or 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 for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non-Potassium-Sparing Diuretics The electrocardiographic 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 beta-agonists with non-potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and β_2 -agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO 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 BREO. **Fluticasone Furoate and Vilanterol:** There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m² basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). **Fluticasone Furoate:** There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m² basis at maternal doses up to 27 mcg/kg/day). **Vilanterol:** There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery There are no adequate and well-controlled human trials that have investigated the effects of BREO during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, BREO should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and β_2 -agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.4 Pediatric Use BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established. In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a

mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. [See Clinical Studies (14.2) of full prescribing information.] Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n = 151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n = 130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.

Effects on Growth Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. [See Warnings and Precautions (5.17); Use in Special Populations (8.4) of full prescribing information.]

8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for asthma included 854 subjects aged 65 years 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 subjects.

8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects [see Clinical Pharmacology (12.3) of full prescribing information].

8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment [see Clinical Pharmacology (12.3) of full prescribing information].

10 OVERDOSAGE

No human overdose data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO 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.

10.1 Fluticasone Furoate Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur [see Warnings and Precautions (5.8)]. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Vilanterol The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Also inform them that currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Not for Acute Symptoms Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta₂-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used. Instruct patients to seek medical attention immediately if they experience any of the following: Decreasing effectiveness of inhaled, short-acting beta₂-agonists; Need for more inhalations than usual of inhaled, short-acting beta₂-agonists; Significant decrease in lung function as outlined by the physician. Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-acting Beta₂-agonists Instruct patients not to use other LABA for COPD and asthma.

Local Effects Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush.

Immunosuppression Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Hypercorticism and Adrenal Suppression Advise patients that BREO may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO.

Reduction in Bone Mineral Density Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Ocular Effects Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

Risks Associated with Beta-agonist Therapy Inform patients of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Hypersensitivity Reactions, Including Anaphylaxis Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO and ELLIPTA are registered trademarks of the GSK group of companies.



BREO was developed in collaboration with Theravance



GlaxoSmithKline
Research Triangle Park, NC 27709

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Revised 8/2016

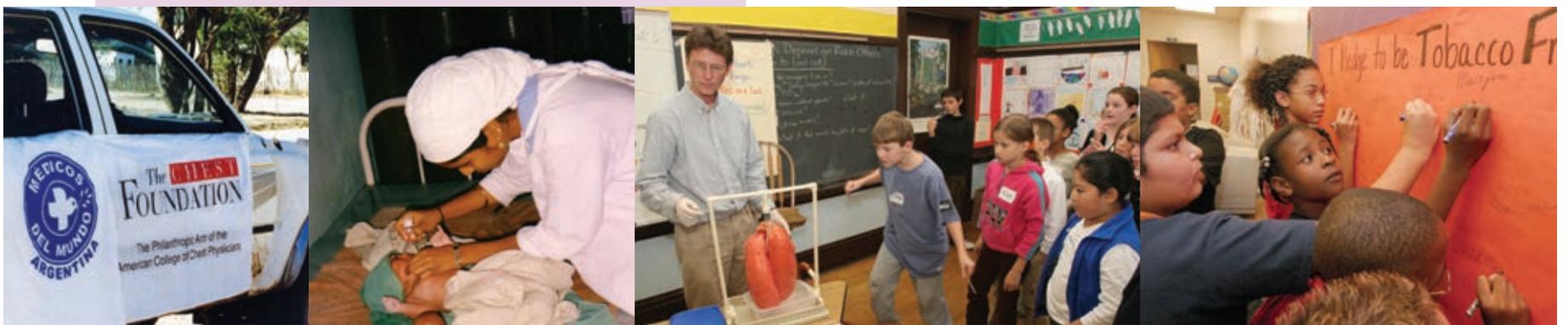
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BRE-7BRS

CHEST FOUNDATION 20TH ANNIVERSARY

CELEBRATING 20 YEARS

AS CHAMPIONS FOR LUNG HEALTH



In 1935, Murray Kornfeld's vision of patients and clinicians working together to advance global lung health inspired the founding of the American College of Chest Physicians. We embraced that same vision 20 years ago when the CHEST Foundation was established as the charitable foundation of the American College of Chest Physicians. Through CHEST Foundation-supported programs, CHEST's 19,000+ members engage in clinical research, participate in community service, and deliver patient education, advancing the lung health of millions of patients in local communities around the world.

Today, as we celebrate our 20th anniversary as the CHEST Foundation, we'd like to say a huge thank you to all our volunteers, donors, and staff who have served as champions for lung health, making the successes of the last 20 years possible!

1996

CHEST Foundation, founded by a strong group of motivated leaders, awards 30+ grants for clinical research, world health partnerships, lectures, and young investigators

1997—

CHEST Foundation film *A Physicians Perspective*, highlighting end-of-life care, wins AMA Freddie Award

1998—

Women & Girls, Tobacco, & Lung Cancer Speaker's Kit developed to target women and children in an anti-tobacco use campaign

1999

CHEST Foundation recognizes 12 winning humanitarian programs with the new Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP

2006—

"Ant E Tobacco" program and "Make the Choice: Tobacco or Health?" toolkits evolved, allowing CHEST members to reach students in elementary schools

2007

CHEST Foundation Case Competition established to encourage teams of students from local universities to develop sustainable organizational models to improve asthma diagnosis and treatment

2008

CHEST Foundation supports AMA Alliance Screen-Out! Program, changing the Motion Picture Association of America's rating system so new movies showing smoking or tobacco use would be rated "R"

2009—

Physicians Speaking For Humanity (PS4H) campaign initiated to appeal to physicians who lecture and/or attend pharmaceutical focus groups to donate their honorariums to the CHEST Foundation

2000—

CHEST Foundation and Cultural Diversity in Medicine NetWork create Educational Guide on Lung Health for Elementary School Children

2001—

Ambassadors Group founded to serve as health advocates, participating in educational programs on tobacco addiction and asthma care

2001

CHEST Foundation established a 9/11 Emergency Response Fund, collecting \$75,000 to support a free smoking cessation program for FDNY

2002—

First winner selected for new Distinguished Scholar program, developed to provide multiyear grants to CHEST members whose projects promise to impact clinical chest and critical care medicine

2002—

CHEST Foundation and Eli Lilly and Company Foundation partner to create Critical Care Family Assistance Program (CCFAP) to better engage family members during a loved one's ICU stay

2003—

Representatives from the American Association of Critical-Care Nurses (AACN) joined the CCFAP advisory team and assisted in the selection of additional program sites

2004

Following major tsunami in southeast Asia, CHEST Foundation set up a disaster relief fund, generating donations to care for victims and help rebuild a small fishing village in Sri Lanka

2005—

After hurricanes Katrina, Rita, and Wilma, CHEST Foundation created Hurricane Relief—Beyond the First Response Matching Gift Fund, to support CHEST members in efforts to serve their patients

**2010**

C. Sola Olopade, MBBS, MPH, FCCP, won his second Humanitarian Award for his work to protect women and children in rural Nigeria from the exposure to indoor pollution. Dr. Olopade continues his efforts in Africa, with funding from the NIH and United Nations Foundation

2011—

CHEST Foundation hosts "OneBreath Luau" raising funds to support the launch of OneBreath.org, part of a new public-facing campaign

2012—

"Beyond Our Walls" campaign launched, seeking support for CHEST's new Innovation, Simulation, and Training Center

2013

First DVT Disease Awareness Month campaign created, which inspired a greater effort in supporting similar campaigns delivering education on topics like COPD, asthma, lung cancer, and sarcoidosis

2014—

CHEST Foundation participated in the FDA's first youth tobacco prevention campaign, "The Real Cost," designed to educate at-risk youth about dangers and impacts of tobacco use

2015

Partnership with American Lung Association initiated to develop up-to-date online patient education guides featuring easy-to-access information on 40 lung health topics

2016

CHEST Foundation names "Champions Circle" Annual Fund giving club, "Founders Society" recognizing CHEST members for cumulative giving, and "Friends of the Foundation" for long-term industry partners

PRESIDENT'S REPORT The Six F's for our most important faculty volunteers

BY WILLIAM F. KELLY, MD, FCCP
CHAIR, EDUCATION

NICKI AUGUSTYN
SENIOR VICE PRESIDENT, EDUCATION

BARBARA PHILLIPS, MD,
MSPH, FCCP
CHEST PRESIDENT 2015-2016

This has been an extraordinary year for CHEST, particularly in the core area of clinical education. In the past fiscal year, we exceeded our educational goals. We set out to reach 10,000 learners through educational programming including live courses and conferences, and online activities; in the end, we served 15,547.



DR. KELLY

Other goals accomplished include demonstrating a significant increase in average learner knowledge acquisition and procedural skills improvement; identifying top



MS. AUGUSTYN

priorities for on-line offerings and delivering five stand-alone on-line modules that can serve as a point of entry to wider audiences; recording professional attendance at CHEST 2015



DR. PHILLIPS

of 5,149 people; offering online training for guideline development and the panelists engaged in CHEST guidelines; achieving an attendance at CHEST World Congress in Shanghai of 2,089; and working with leading Chinese medical societies to see the China-CHEST Pulmonary and Critical Care Medicine Fellowship Program formally adopted by the government in China as one of the four first-ever subspecialty training programs to be implemented nationwide.

This is a lot!

These accomplishments depend on intense work and collaboration between our incredibly talented faculty and volunteers from among CHEST membership and CHEST's amazing professional staff of 105 employees,

of which 28 are dedicated full time to the development and delivery of education and best practices. Through this partnership, we continue to meet CHEST's mission: To champion the prevention, diagnosis, and treatment

of chest diseases through education, communication, and research.

Without these dedicated women and men, CHEST would be utterly unable to complete its mission. Our faculty work in a vast array of oppor-

tunities, including writing questions for SEEK, serving as a content expert for guidelines, proposing and delivering sessions at CHEST, running Board Review courses, recording videos, facilitating hands-on simu-

DELAY PAH PROGRESSION TO...



INDICATION

UPTRAVI 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

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.

Please see additional Important Safety Information on adjacent page.

ADD | **Uptravi**
selexipag
tablets | 200/1600 mcg



lation sessions, and more. While intrinsically gratifying, there are many difficult elements to such work, requiring commitment that begins long before the delivery of an event or the launch of a new activity. Reviewing existing literature and knowledge on a topic to determine whether an activity will meet the needs of our

membership; coming up with valid learning objectives; generating just the right multiple choice questions and other assessments to measure our success at helping learners reach those objectives; peer reviewing content to ensure we're teaching to the latest science and established best practices; and then measuring learner

outcomes – these elements put the “state of the art” into CHEST’s internationally recognized state-of-the-art educational program.

To achieve our mission, we have been asking CHEST’s valiant and dedicated volunteers to do more than ever before, and some of what we have asked them to do has been

frustrating, tedious, and less than rewarding, often due to imperfect technology platforms we’ve asked our volunteers to use; the disconnect between the educational goals we have set and the implementation of the clear processes, communication, and on-boarding of staff required to

Continued on following page

UPTRAVI® (selexipag)— The Only Oral PAH Therapy Targeting the Prostacyclin Pathway Proven to Delay Disease Progression¹

RESULTS FROM GRIPHON, THE LARGEST OUTCOMES TRIAL
EVER CONDUCTED IN PAH (N=1156)

GRIPHON was a multicenter, long-term, double-blind, placebo-controlled, parallel-group, event-driven phase 3 study in 1156 patients (UPTRAVI: n=574; placebo: n=582) with symptomatic PAH (nearly all WHO FC II-III at baseline). The median treatment duration for the UPTRAVI group was 1.4 years.

40% RISK REDUCTION IN DISEASE PROGRESSION IN PATIENTS TREATED WITH UPTRAVI (p<0.0001)

- Reductions in PAH-related hospitalization and other disease progression events* drove the overall reduction

PRIMARY ENDPOINT EVENTS UP TO THE END OF TREATMENT:

A primary endpoint event was experienced by 27.0% of UPTRAVI-treated patients vs 41.6% 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%), and PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%).

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Adverse reactions occurring more frequently (≥3%) on UPTRAVI compared to placebo 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

Strong CYP2C8 inhibitors

Concomitant administration with strong inhibitors of CYP2C8 (eg, gemfibrozil) may result in a significant increase in exposure to selexipag and its active metabolite. Avoid concomitant use.

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.

*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; WHO=World Health Organization.

Reference: 1. UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc. December 2015.

Visit www.UPTRAVI.com to learn more and download the Patient Enrollment Form



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Continued from previous page

support them; and the lag of recognition proportionate to the nature of these new asks.

To acknowledge the priceless contributions made by our faculty volunteers, CHEST staff and volunteer leadership have developed a Faculty

& Volunteer Treatment Action Plan, recently approved by the CHEST Board of Regents. This is part of our comprehensive “six F’s” plan:

Formal recognition and rewards
Recognition and rewards: different meanings – but both important.
Recognition is expressing gratitude

for an expected job that was well done and includes a *formal* thank-you. Rewards are additional, tangible benefits for exceptional services. We now have enhanced guidelines for travel, honoraria, and amenities for our volunteer faculty. Also of note, two new awards will be bestowed annually beginning at CHEST 2016

Los Angeles – the Early Career Clinician Educator Award and the Master Clinician Educator Award. These are some additional ways we will more appropriately highlight the people who have helped make us CHEST, the leader in clinical education in chest medicine.

Feedback

In addition to learner satisfaction data, CHEST provides an unprecedented level of learner outcomes data to our faculty. We are even introducing a new peer-review of teaching (PRT) program, so faculty can get even more feedback from expert colleagues.

Faculty Development

As an education-focused organization, training and development play a foundational role. We are working to develop a comprehensive clinician educator program that will grow our bench of faculty. A newly launched database will more proactively track CHEST teaching opportunities and match interested members with these opportunities.

Face Time

Easy access to leadership and staff is important. We are implementing staff training that will better position all CHEST employees to more effectively facilitate and support the work we ask of our faculty. On another front, we are engaged in identifying new, user-friendly systems for session submission, conflict of interest disclosure, and review, as well as developing content.

Food

It is a simple but well-established fact that having a stocked lounge area for busy faculty on the run between teaching sessions enhances efficiency, communication, camaraderie, and overall morale.

Fun

The fun of discovering better ways to take care of our patients, be it from the teacher or learner perspective, in an engaging, effective learning environment is and always has been at the center of what we do.

CHEST’s volunteer leaders, in service to their peers, the field, and the organization, have risen repeatedly to many challenges. We need to do a better job of rewarding and recognizing their irreplaceable contributions. The above initiatives, and others, we hope, will help demonstrate to our most precious resource, our member-faculty, that we truly value and appreciate their invaluable contributions on behalf of CHEST. Stay tuned and stay with us.



Rx Only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

UPTRAVI 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%).

DOSAGE FORMS AND STRENGTHS

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg

CONTRAINDICATIONS

None.

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 ≥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

Strong CYP2C8 Inhibitors

Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite. Avoid concomitant administration of UPTRAVI with strong inhibitors of CYP2C8 (e.g., gemfibrozil) [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 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.

UPTRAVI® (selexipag)

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:

No clinically relevant effects of sex, race, age, or body weight on the pharmacokinetics of selexipag and its active metabolite have been observed in healthy subjects or PAH patients.

Age:

The pharmacokinetic variables (C_{max} and AUC) were similar in adult and elderly subjects up to 75 years of age. There was no effect of age on the pharmacokinetics of selexipag and the active metabolite in PAH patients.

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

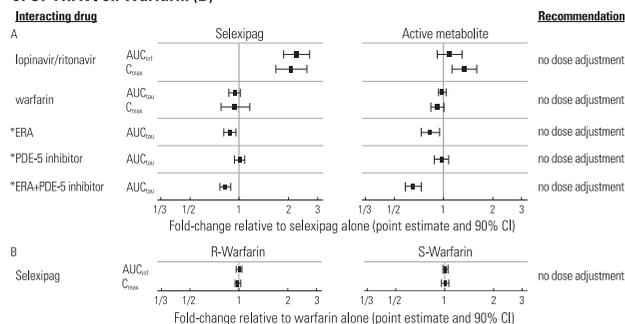
Selexipag is hydrolyzed to its active metabolite by hepatic carboxylesterase 1. Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates 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 strong inhibitors of CYP2C8 (such as gemfibrozil) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite [see *Drug Interactions*].

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
ACT20151221b

Reference: 1. UPTRAVI full Prescribing Information.

Actelion Pharmaceuticals US, Inc. December 2015.

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This Month in CHEST: Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP
EDITOR IN CHIEF, CHEST

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. By Dr. J. Corren, et al.

Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase III Study. By Dr. L. Bjeramar, et al.



A Critical Review of the Quality of Cough Clinical Practice Guidelines. By Dr. M. Jiang, et al.

Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With

Community-Acquired Pneumonia. By Dr. W. H. Self, et al.

Evaluation of Pulmonary Nodules: Clinical Practice Consensus Guidelines for Asia. By Dr. C. Bai, et al.

Occupational and Environmental Contributions to Chronic Cough in Adults: Chest Expert Panel Report. By Dr. S. M. Tarlo, et al, on behalf of the CHEST Expert Cough Panel.

SUNRISE Program in India

Recently, CHEST completed the SUNRISE (Respiratory Initiative in Scientific Education) live learning program in India. More than 800 physicians attended and gained knowledge in asthma, COPD, ILD, and sleep over a 3-day period in three different cities – Bengaluru, Kolkata, and Delhi. According

to the feedback report, more than half of the participants rated the program as highly above average, and approximately 70% will change something in their practice based on what they learned. Suggestions for next year's program, including content and speakers, are being considered.



Diego Maselli, MD, FCCP, addresses attendees in Bengaluru.



Attendees at the SUNRISE Program held in Delhi.

Three options for MIPS

MACRA from page 1

ing medication, you need to take this reprieve as an opportunity to familiarize yourself with the MIPS requirements as I expect this might not happen again. Most importantly, remember the final rule will provide essential details of the new program that are lacking from this early announcement.”



Independent practice will become unrealistic for those who experience the greatest financial penalty.

DR. MATHERS

James A.L. Mathers Jr., MD, FCCP, pointed out that “under the MIPS system, based on comparison with peer practices, roughly a quarter of the providers choosing to remain in fee for service will see a significant financial penalty at the end of each year. The escalating financial penalties will make independent practice unrealistic for the 25% of practices that

experience the greatest financial penalty,” Dr. Mathers said. While recent CMS announcements “are encouraging, no details have been released and any relief in reporting requirements will be short term.”

Nitin Damle, MD, president of the American College of Physicians, said in a statement that the ACP is pleased that “CMS plans ... to give physicians more options to participate in the quality payment programs in 2017 without being at risk of negative adjustments. These changes are consistent with recommendations made by ACP and other physician stakeholders to exempt small practices from negative adjustments and to provide more flexible options for practices of all sizes to be successful.”

Early details of the plan were announced in September in a blog post by CMS Acting Administrator Andy Slavitt.

The agency is currently reviewing comments on its proposed regulations to implement MACRA (Medicare Access and CHIP Reauthorization Act of 2015), with a final rule expected in November.

The QPP required CMS to divide physician compensation into two main tracks, the MIPS, which applies to those wishing to continue billing fee for service, and Advanced Alternative Payment Models (APMs).

Those who choose the MIPS track now have three options for when they must start reporting data next year. Data reported in 2017 will serve as the benchmark for bonus payments paid in 2019.

Option 1

Report “some data” in 2017. Doctors who report some data to the QPP will not face a Medicare pay cut. CMS considers even this low level of reporting a test for whether physicians will be ready for more intense MACRA involvement in 2018 and 2019. Exactly how much “some data” is currently is not defined.

Option 2

Participate for part of 2017. Those who choose to report data to QPP for some of the year also will be testing their systems for future MACRA compliance and may end up with a small Medicare pay increase. Again, the duration of reporting was not defined by the CMS at press time.

Option 3

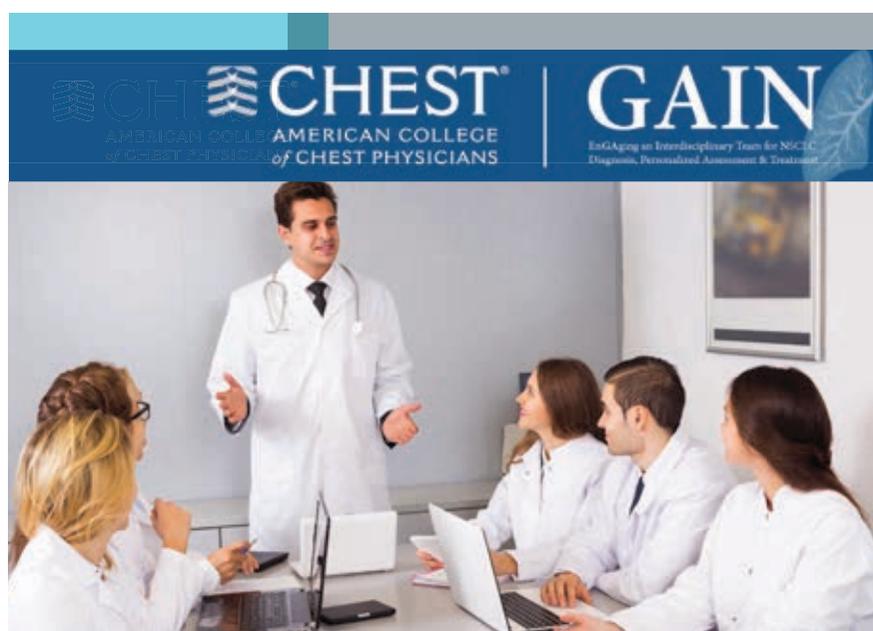
Participate for the full year. Doctors who begin to report data from all parts of QPP on Jan. 1 will be eligible for a “modest” Medicare pay increase in 2019. Data on quality measures, use of technology, and practice improvement must be reported.

“While the recent comments by Acting Administrator Slavitt are encouraging, no details have been released and any relief in reporting requirements will be short term,” according to Dr. Mathers.

For those who are eligible for participation in APMs, that track will begin Jan. 1, 2017.

The American Medical Association commended federal officials “for listening to physicians’ concerns about the timeline that was originally proposed for MACRA,” AMA President Andrew Gurman, MD, said in a statement. “The AMA believes the actions that the administration announced today will help give physicians a fair shot in the first year of MACRA

Continued on following page



Collaborators

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Registration for our 2017 live learning courses will open in November. Stay tuned for our updated calendar in next month's CHEST.

Twice as much time spent on EHRs as on patients

BY GREGORY TWACHTMAN
Frontline Medical News

Physicians are spending twice as much time on electronic health records as they are face to face with patients, according to a new study by the American Medical Association.

Researchers observed 57 physicians in four specialties (family medicine, internal medicine, cardiology, and orthopedics) and found that for every hour of direct clinical face time with patients, nearly 2 additional hours is spent on EHR and desk work within the clinic day. Additionally, based on



EHR regulations need to focus on reducing the time-cost of providing care on their platforms and provide flexibility.

DR. SINSKY

diaries kept by 21 of the participating physicians, another 1-2 hours of personal time were spent each night doing additional computer and clerical work, according to the study published Sept. 5 in *Annals of Internal Medicine* (2016. doi: 10.7326/M16-0961).

“Over the years, doctors have recognized that more and more of their time was spent on nonpatient care, activities but probably haven’t recognized the magnitude of that change,” Christine Sinsky, MD, vice president of professional satisfaction at the AMA and lead author on the study, said in an interview. “Our study was able to help to quantify that and paint that picture.”

Overall, physicians spent 27% of

their day dealing directly with patients, while 49% of the time was spent on EHR and desk work. In the examination room with patients, physicians spent 53% of time on direct clinical face time and 37% on EHR and desk work.

The situation “is the cumulative effect of many, many well-intended efforts that individually might have made sense, but taken collectively have paradoxically made it harder for physicians to deliver quality of care and harder for patients to get the quality of care they deserve,” she said.

EHR development should be focused on reducing the time-cost of providing care on their platforms, Dr. Sinsky recommended. She noted that for her practice, it takes 32 clicks to order and record a flu shot. “I think vendors have a responsibility to minimize time, to minimize clicks involved in a task.”

She added that “regulators have a responsibility to not just add more and more regulations without first identifying the time-cost of complying with that regulation and without adding up the total cost of complying with regulation.”

Future regulations on EHRs must add flexibility when it comes to who is entering information into the system, she said. “Many regulations are either written with the explicit statement – or it is implied or an institution might overinterpret the regulation – that the physician is the one who must do the keyboarding into the record,” she said, noting that although not primarily studied in the research, preliminary data suggests that doctors who had documentation support were able to spend more time with their patients.

Finally, physicians themselves need



to be stronger advocates for the changes they need to enable them to better serve their patients.

In addition to Dr. Sinsky, three other study authors are employed by AMA,

which funded the study.

No other financial conflicts were reported.

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VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP, comments: This study finally quantified what many physician have known since EHRs were introduced ... patient time is being sacrificed to computer time. Perhaps equally or more important is the sacrifice of “family time” later in the evening. The discussion in the paper suggests that the loss of time related to EHRs may be contributing to the current level of physician dissatisfaction. The effect of age was also not a factor that was directly assessed in the study but the implication was that older physicians might be less efficient with technology compared with their younger counterparts. I suspect both of these suppositions

may be accurate. I would, however, suggest an alternative method to deal with the issue of physician inefficiency with technology. Rather than attempting to fit square (pulmonologist), triangular (obstetrician), pentagonal (surgeon), etc, pegs into a round hole (EHR), regulators should craft rules that compel the multiple EHR vendors to provide platforms that limit clicking and scrolling to maximize patient/physician interaction. Thirty-two clicks for a flu shot is a bit ridiculous. Additionally, prior to mandating meaningful use, regulators should verify that it is truly meaningful to patient care and doesn’t detract from physicians’ time with patients.

Continued from previous page

implementation. This is the flexibility that physicians were seeking all along.”

The new flexibility may not be a good thing, particularly for larger group practices that are ready to fully participate in MACRA as of Jan. 1, some said.

“This flexibility is especially important for small provider groups that may have legitimate logistical issues around MACRA’s reporting requirements,” Donald Fisher, PhD, president and CEO of AMGA, said in a statement. (AMGA was formerly known as the American Medical

Group Association.)

“However, our membership is deeply concerned that the creation of these new reporting options will have the unintended result of penalizing the very provider groups that have made the largest investments to meet MACRA’s goals of better quality, improved clinical practice activities, better use of electronic medical records, and lower resource use. These groups have already begun the transition from volume to value, and it is disappointing the rewards for their effort will be compromised rather than rewarded, as was MACRA’s stated purpose by Congress and

the administration,” Dr. Fisher said.

By offering options for compliance, the CMS could potentially limit the amount of bonus payments in order to meet MACRA’s budget-neutral requirements, according to Chet Speed, vice president of public policy at AMGA. There will be no potential penalties that would offset bonuses for organizations that are performing at a high rate, which could result in having to lower the maximum bonuses an organization would be eligible to receive.

“You’ve compressed rewards to a level where it just penalizes those who have made the investments” in

upgrading their systems to prepare for the Jan. 1 start date, Mr. Speed said.

He emphasized that the CMS could still address this and make the full bonus payments available to those who are prepared to participate on Jan. 1, but that will not be known until the final rule is published.

He applauded the agency’s efforts in continually reaching out to the physician community throughout the MACRA development process and said he is hopeful there will be resolution to these concerns in the final rule.

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INTRODUCING

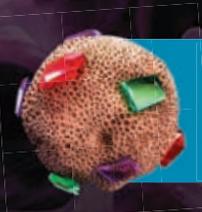
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New method proposed for phenotyping COPD patients

BY TED BOSWORTH
Frontline Medical News

LONDON – Based on readily available clinical data, patients with chronic obstructive pulmonary disease (COPD) can be placed into five phenotypes with different characteristics and risk profiles, according to data generated by a cluster analysis and presented at the European Respiratory Society International Congress 2016.

The algorithm that places patients into these phenotypes was developed from a cluster analysis, reported Pierre-Regis Burgel, MD, PhD, professor of respiratory medicine, Université René Descartes, Paris. Mortality rates at 3 years for these phenotypes ranged from 2.6% to 49.5%.

“We think that this could be the basis for recognizing clinically distinct COPD phenotypes and designing better tailored management,” Dr. Burgel explained. “We also think it has potential use in routine clinical assessment.”

To create these phenotypes, data from 2,049 COPD patients enrolled in a French-Belgian collaborative cohort were evaluated with Classification And Regression Tree (CART) analyses. The five phenotypes were derived from symptom burden, respiratory function, relative age, and

presence of comorbidities.

Based on these characteristics, “a set of clinical rules” to phenotype patients was developed, according to Dr. Burgel. This algorithm was then further validated with the 3,651 COPD patients enrolled in the prospective COPD Cohorts Collaborative International Assessment (3CIA) initiative.

“We think [this algorithm] could be the basis for recognizing clinically distinct COPD phenotypes and designing better tailored management. We also think it has potential use in routine clinical assessment,” said Dr. Burgel.

The two initial branches in the algorithm are created by dividing patients into those with and without cardiovascular comorbidities or diabetes. In those without cardiovascular disease, the phenotypes are defined by relative symptom severity, using cut-off scores from the modified Medical Research Council (mMRC) dyspnea assessment tool and relative degrees of lung function impairment as measured with forced expiratory volume in 1 second (FEV₁).

In those with cardiovascular disease or diabetes, mMRC-defined symptoms and FEV₁-defined lung function impairment also create decision points in the algorithm, but age and body mass index (BMI) are additional variables that direct patients to a specific phenotype. Class 4 and 5 are reached in the absence of cardiovascular disease or diabetes only, while cardiovascular disease is a prerequisite to reach Classes 4 and 5. Class 2 is the only phenotype that can be reached through the algorithm irrespective of the presence or absence of cardiovascular disease.

Using this algorithm, each of the phenotypes was associated with similar relative hierarchy in mortality in the two cohorts, even though mortality rates for each phenotype were consistently lower in the 3CIA group.

For class 1, which was reached by patients with cardiovascular disease or diabetes, the greatest symptom burden, and the lowest lung function, the mortality rates at 3 years were 49.5% and 23.2% for the French-Belgian and 3CIA cohorts, respectively.

For class 4, which was also defined by the greatest symptom burden and the lowest lung function without cardiovascular disease or diabetes the mortality rates were 45.3% and 27.3%, respectively. The lowest mortality rates, which were 2.6% and 4.0%, respectively, were found in the

class 5 phenotype, which contained patients with a low symptom burden (mMRC less than or equal to 1), relatively good lung function (FEV₁ greater than or equal to 60%), and no history of cardiovascular disease or diabetes.

In classes 2 and 3, the mortality rates fell in between those of the lowest- and highest-risk phenotypes. Specifically, these 3-year mortality rates were 22.9% and 24%, respectively, in the French-Belgian cohort, and 11.1% and 14.1%, respectively, in the 3CIA cohort.

The consistency of the hierarchy of outcomes in the two cohorts provides the basis for suggesting that these phenotypes are effective for categorizing relative risk, according to Dr. Burgel. He believes that the phenotypes are clinically important, and he emphasized that the algorithm relies on clinical information that is already routinely collected and readily accessible.

“There is growing awareness that COPD phenotypes are important and are likely to be valuable in managing patients,” Dr. Burgel explained. “We feel that we have created simple rules for allocating patients that we think will be useful for research and for clinical application.”

Dr. Burgel reported financial relationships with a number of drug companies.

Modified COPD assessment simplifies risk prediction

BY TED BOSWORTH
Frontline Medical News

LONDON – Four questions from the eight-question COPD Assessment Test (CAT) provide about the same prognostic accuracy in patients with chronic obstructive pulmonary disease (COPD) as does the full CAT, according to an analysis presented at the annual congress of the European Respiratory Society.

When the four- and eight-question versions were compared for exacerbation and other clinical outcomes over a 1-year period of follow-up, “both strategies demonstrated similar discrimination,” reported Carlos H. Martinez, MD, division of pulmonary and critical care medicine, University of Michigan Health System, Ann Arbor.

The CAT is an eight-item tool for evaluating the health status of patients with COPD as well as for predicting risk of COPD-related events, particularly exacerbations. The test is designed for self-administration by patients. For each of the questions, which address symptoms and activity limitations, patients are asked to answer on a scale ranging from one (indicating no clinical burden) to five (indicating severe burden). Based on the

maximum score of 40, a score below 10 signifies a low impact from COPD, a score of 10-20 signifies a medium impact, and a score above 20 signifies a high impact.

In this study, a simplified version of the CAT that employed just four of the questions was evaluated in 880 participants in the observational SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study), which was funded by the National Heart, Lung, and Blood Institute and has prospectively enrolled COPD patients at seven participating centers. Ever-smokers from SPIROMICS were eligible for this analysis if they had a forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ratio of greater than or equal to 0.70 and an FVC above the lower limit of normal.

The four questions that were retained were about cough, phlegm, chest tightness, and breathlessness. The four questions that were eliminated were about activity limitation, sleep, energy, and the effect of lung symptoms on willingness to leave the house.

With the traditional test, using a cut point of greater than or equal to 10, 51.8% were classified as having a significant COPD burden. In

this group, 15.3% experienced one or more exacerbations during 1 year of follow-up. With the simplified version focused on respiratory-related symptoms alone and using a cut point of greater than or equal to 7, 45.8% were classified as having a significant COPD burden, and 15.6% had one or more exacerbations during the same period of follow-up.

“The two strategies largely identified the same individuals,” according to Dr. Martinez, who reported the agreement as 88.5% (Kappa 0.77; *P* less than .001). There was no difference in the area under the curve (AUC) to predict exacerbations at 1 year. In further analysis, “subjects identified by either method also had more depression and anxiety symptoms, poorer sleep quality, and greater fatigue [than did the lower risk group],” Dr. Martinez added.

An AUC ROC (receiver operating characteristic) statistical analysis to compare the traditional and abbreviated CATs for cross-sectional associations showed close agreement. The values were nearly identical for such variables as dyspnea, impairment as measured with the 6-minute walking distance (6MWD) test, and quality of life as measured by the St. George’s Respiratory Questionnaire.

Antibiotics overprescribed for asthma inpatients

BY DEEPAK CHITNIS
Frontline Medical News

Antibiotics are overprescribed in asthma-related hospitalizations, even though guidelines recommend against prescribing antibiotics during exacerbations of asthma in the absence of concurrent infection, reported Peter K. Lindenauner, MD, MSc, of Baystate Medical Center in Springfield, Mass., and his colleagues.

They examined the hospitalization records of 51,951 individuals admitted to 577 hospitals in the United States between 2013 and 2014 with a principal diagnosis of either asthma or acute respiratory failure combined with asthma as a secondary diagno-



These findings suggest a significant opportunity to improve patient safety and reduce the spread of resistance.

DR. LINDENAUER

sis. Each patient type and the timing of antibiotic therapy was noted.

A total of 30,226 of the 51,951 patients (58.2%) were prescribed antibiotics at some point during their hospitalization, while 21,248 (40.9%) were prescribed antibiotics on the first day of hospitalization, without “documentation of an indication for antibiotic therapy.”

Macrolides were most commonly prescribed, given to 9,633 (18.5%) of patients, followed by quinolones (8,632, 16.1%), third-generation cephalosporins (4,420, 8.5%), and tetracyclines (1,858, 3.6%). After adjustment for risk variables, chronic obstructive asthma hospitalizations were found to be those most highly associated with receiving antibiotics (odds ratio 1.6, 95% confidence interval 1.5-1.7).

“Possible explanations for this high rate of potentially inappropriate treatment include the challenge of differentiating bacterial from non-bacterial infections, distinguishing asthma from chronic obstructive

pulmonary disease in the acute care setting, and gaps in knowledge about the benefits of antibiotic therapy,” the authors posited, adding that these findings “suggest a significant opportunity to improve patient safe-

ty, reduce the spread of resistance, and lower spending through greater adherence to guideline recommendations.”

The National Heart, Lung, and Blood Institute and Veterans Affairs

Health Services Research and Development funded the study. Dr. Lindenauner and his coauthors did not report any relevant financial disclosures.

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Benralizumab reduces severe asthma events

BY SARA FREEMAN
Frontline Medical News

LONDON – The investigational treatment benralizumab significantly reduced the number of exacerbations

that patients with severe, uncontrolled asthma experienced during the course of a year in two phase III studies.

In the SIROCCO and CALIMA trials, which altogether involved

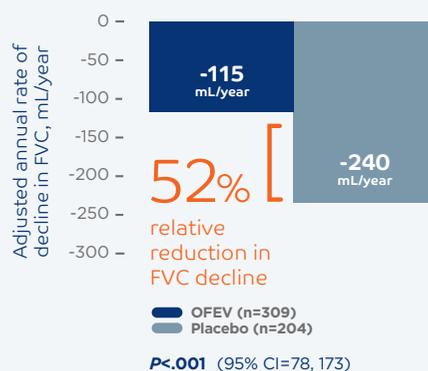
more than 2,000 adult patients, the annual exacerbation rate (AER) was cut by 28%-51%, compared with placebo when benralizumab was added to standard combination therapy of an inhaled corticosteroid

(ICS) and a long-acting beta-agonist (LABA).

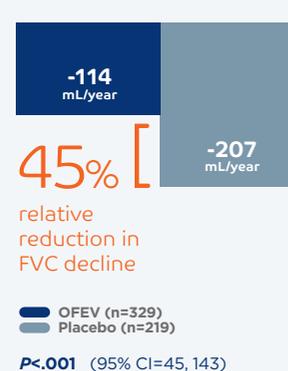
Benralizumab treatment was also associated with significant improvements in lung function (up to 159 mL increase in FEV₁), and reduced daily

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

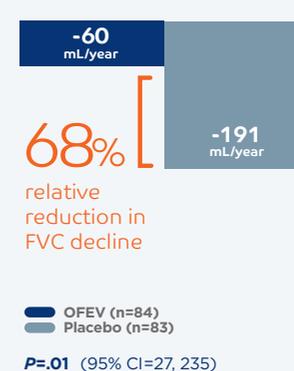
INPULSIS®-1 (Study 2)^{3,4}



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.



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asthma symptoms of wheeze, cough, and dyspnea versus placebo.

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Benralizumab has been shown to rapidly and almost completely deplete the number of eosinophils in the blood, airways, and bone marrow, said Dr. Bleecker.

studies were published in full online in *The Lancet* to coincide with their presentation at the annual congress of the European Respiratory Society.

Benralizumab is a humanized, monoclonal antibody that has been shown to rapidly and almost completely deplete the number of eo-

sinophils in the blood, airways, and bone marrow, Eugene R Bleecker, MD, who presented the results of the SIROCCO study, explained at the meeting.

Dr. Bleecker, who is the director of the Center for Genomics and Personalized Medicine Research at Wake
Continued on following page

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

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In INPULSIS® trials, there was not a statistically significant difference in all-cause mortality for OFEV compared with placebo.⁵

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.



Continued from previous page

Forest University in Winston-Salem, N.C., observed that benralizumab “works a little bit differently” than other interleukin (IL)-5–targeting monoclonal antibodies, such as mepolizumab and reslizumab. Rather than target the IL-5 ligand itself,

benralizumab binds to IL-5 receptors present on the surface of eosinophils. This action activates natural killer cells, which then destroy the eosinophils via antibody-dependent cell-mediated cytotoxicity.

Phase IIb data have already shown a benefit for benralizumab versus placebo in patients with uncontrolled

asthma with high (300 cells/mL or greater) eosinophil counts in the blood. The aim of the SIROCCO and CALIMA phase III trials was thus to examine the efficacy and safety of the novel agent further in this patient population.

In SIROCCO, 1,205 patients were randomized, and 1,306 were random-

ized in CALIMA. Key inclusion criteria were physician-diagnosed asthma requiring ICS/LABA therapy and at least two exacerbations in the past 12 months. Patients also needed to be symptomatic during a 4-week run-in period before being randomized to one of three study groups. The groups included one that received

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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TREAT NOW. SLOW PROGRESSION.

benralizumab at a subcutaneous dose of 30 mg every 4 weeks; another that received benralizumab at a subcutaneous dose of 30 mg every 4 weeks for the first three doses then a 30 mg dose or placebo injection alternating every 4 weeks; and a third group that received placebo injections every 4 weeks.

The mean age of patients in both studies and across treatment arms was broadly similar, ranging from 47 to 50 years. Around two thirds of the study population was female, with similar baseline characteristics.

The primary endpoint was the AER in patients with a blood eosino-

phil count of 300 cells/mcL or higher. In SIROCCO this was measured at 48 weeks and in CALIMA at 56 weeks.

The respective AERs for placebo and for the 4- and 8-week dosing regimens of benralizumab were 1.33, 0.73, and 0.65 in SIROCCO and 0.93, 0.6, and 0.66 in CALIMA. This rep-

resented a 45% reduction in the AER for the 4-week and a 51% reduction for the 8-week regimens of benralizumab versus placebo in SIROCCO, and a 36% and 28% reduction, respectively, in CALIMA.

There was a large placebo effect and the overall population recruited

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).

DOSAGE 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 system 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

Continued from previous page

into CALIMA may have had less severe asthma than the patients who participated in SIROCCO, the principal investigator for CALIMA, Mark FitzGerald, MD, pointed out during a press briefing organized by AstraZeneca. “But when you look at the

composite of both studies together, you can see that the results are quite robust,” said Dr. FitzGerald, the director of the Centre for Lung and Heart Health at Vancouver Coastal Health Research Institute.

There was also some evidence that patients who had three or more prior exacerbations fared better, he

said, highlighting the importance of defining the patient population who may benefit the most from this treatment.

Something that needs to be investigated further is why patients given the 8-week benralizumab regimen seemed to do better, at least numerically, than those given the 4-week

regimen. Dr. FitzGerald suggested that “because eosinophil cells are such a powerful driver of disease, perhaps you may not actually need to be treated as frequently as historically we might have done.”

Other similar biologic agents need dosing every 2 to 4 weeks, but perhaps every 8 weeks is a possibility in the future for benralizumab. A lot can be learned from how biologics are used in rheumatology, he suggested, where treatments have started being given less frequently, because the biology of the various

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. **Infertility:** 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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OF-BS-2-16 (2-16) PC-OF-0365-PROF

Rx only



Why 8 weeks of benralizumab seemed better for patients than 4 weeks of benralizumab needs to be investigated.
DR. FITZGERALD

rheumatic diseases is now better understood.

Any adverse event was reported by a similar percentage of actively-treated (71%-75%) and placebo-treated (73%-78%) patients. The frequency and nature of other adverse events were similar to placebo.

The SIROCCO and CALIMA trial data will form part of AstraZeneca's U.S. and EU regulatory submissions later this year for benralizumab as a treatment for severe, uncontrolled, eosinophilic asthma.

“Potentially, when it becomes available, benralizumab will provide a new therapeutic option for this class of patient.” Dr. FitzGerald said.

Benralizumab is also being investigated as a possible treatment for patients with less severe eosinophilic asthma in the BISE phase III study and as an option for those with severe chronic obstructive pulmonary disease who have high levels of eosinophils in the phase III VOYAGER program.

AstraZeneca and Kyowa Hakko Kirin funded the studies.

Dr. Bleecker is the principal investigator for the SIROCCO trial and disclosed receiving research funding or consulting for AstraZeneca-MedImmune, Boehringer Ingelheim, Genentech/Roche, GlaxoSmithKline, Johnson & Johnson (Janssen), Merck, Novartis, Sanofi, Cephalon/Teva, and Regeneron-Sanofi.

Dr. FitzGerald disclosed acting as an advisory board participant, receiving funding or fees, or both from AstraZeneca, ALK Abello, Boehringer Ingelheim, Hoffman-La Roche, Genentech, GlaxoSmithKline, MedImmune, Merck, Novartis, and Teva.

RPL-554 adds to short-acting drugs' benefits in COPD

BY SARA FREEMAN
Frontline Medical News

LONDON – Improved lung function was seen in patients with chronic obstructive pulmonary disease (COPD) when an inhaled dual phosphodiesterase (PDE) inhibitor, RPL-554, was used on top of standard short-acting treatment in a single-center, crossover study.

There was a 51% increase in the peak forced expiratory volume in 1 second (FEV₁) from baseline to the time of measurement up to 12 hours later in patients given RPL-554 in addition to the short-acting beta2-agonist (SABA) salbutamol versus the SABA alone. A benefit also resulted from adding RPL-554 to the short-acting muscarinic antagonist (SAMA) ipratropium. Taking this second combination of drugs resulted in a 66% higher FEV₁, when compared with taking the SAMA alone (*P* less than .001 comparing the combinations with the SABA or SAMA alone).

“We were primarily interested to know if giving this novel drug in addition to a beta-agonist or antimuscarinic could produce more bronchodilation, and that’s what we saw,” said David Singh, MD, of the University of Manchester (England), who presented the study findings at the annual congress of the European Respiratory Society.

In addition to inducing “significant and clinically relevant” additional bronchodilation, a single dose of RPL-554 was found to increase lung volumes when administered on top of standard-of-care bronchodilators. The peak forced vital capacity (FVC) increased by 79.5% when RPL-554 was added to salbutamol and by 43.2% when it was added

to ipratropium. There were also improvements in the baseline residual lung volume and in airway conductance.

RPL-554 is a novel inhaled dual PDE-3/4 inhibitor under investigation in the treatment of both COPD and asthmatic patients. “This is a reformulation of RPL-554, delivered by nebulization,” Dr. Singh observed. It has been shown to have both anti-inflammatory and bronchodilatory properties



in clinical studies, he added, with the latter action thought to be additive to beta-agonists and synergistic with antimuscarinic agents according to preclinical data.

The aim of the study was to look at the potential additive or synergistic bronchodilatory effects of RPL-554 in a clinical study for patients who had moderate to severe COPD. A total of 36 patients (19 men and 17 women) were recruited; 30 completed the study. The mean age of the recruited patients was 61 years; mean body mass index was 27.7 kg/m², mean baseline FEV₁ was 50.4% or 1.44 L, and the patients exhibited a mean increase in FEV₁ of 17.7%, 30 minutes after being given salbutamol or ipratropium at screening. The latter “gives you an idea of the reversibility of the popu-

lation,” Dr. Singh said.

Six treatment options were compared: salbutamol 200 mcg, salbutamol 200 mcg plus RPL-554 6 mg, ipratropium 40 mcg, ipratropium 40 mcg plus RPL-554 6 mg, RPL-554 6 mg, and placebo. At each treatment visit patients were dosed, in a double-blind fashion, with salbutamol, ipratropium, or placebo via a metered-dose inhaler (MDI), and then randomized to receive either inhaled RPL-554 or a placebo via a nasal nebulizer. Spirometry was performed before and up to 12 hours after treatment, and plethysmography was performed before and at 1 and 4 hours after dosing.

The addition of RPL-554 to standard bronchodilator therapy was associated with a faster onset of bronchodilation when compared to either the SABA or SAMA as monotherapies – at 3.6 minutes when added to salbutamol versus 5.2 minutes for the SABA alone, and 4.2 minutes when added to ipratropium versus 18.4 minutes for the SAMA alone. Used alone, however, RPL-554 had an onset of effect of 14.3 minutes.

Overall, the single-doses of RPL-554 used were well tolerated when given alone or in combination with the other treatments. “Obviously with a PDE-3 inhibitor we want to be careful about cardiovascular changes and monitor that, but we did not see anything,” Dr. Singh reported.

Verona Pharma Plc sponsored the study. Dr. Singh reported receiving sponsorship, honoraria, or research funding from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Skyepharma, Takeda, Teva, Theravance, and Verona Pharma Plc.

Artificial intelligence bests physicians' diagnoses

BY TED BOSWORTH
Frontline Medical News

LONDON – In a proof-of-principle study, artificial intelligence (AI) led more frequently to the correct diagnosis of underlying lung disease than did physicians' use of standard algorithms, such as those recommended by the American Thoracic Society and the European Respiratory Society, according to late-breaker data presented at the annual congress of the European Respiratory Society.

“The beauty of this approach is that artificial intelligence can simulate the complex reasoning that clinicians use to reach their diagnosis but in a more standardized and objective fashion, so it removes any bias,” reported Wim Janssens, MD, PhD, of the division of medicine and respiratory rehabilitation at University of Leuven (Belgium).

The AI employed in this study was based on a subfield of computer science that relies on patterns within statistics to build decision trees. Often

called machine learning, this type of AI grows smarter as it learns from the patterns it finds in the data provided.

In this case, the AI was designed to provide diagnoses for lung diseases based on patterns drawn from clinical and lung function data. The computer-based choices were compared to diagnoses reached by clinicians. The final diagnoses were validated by a consensus of expert clinicians.

“The computer-based choices were in almost all cases better than the choices made by standard diagnostic algorithms,” reported Marko Topalovic, PhD, a researcher in AI who is affiliated with the University of Leuven. Dr. Topalovic presented the data at the ERS.

The study involved 968 patients presenting with lung symptoms to a pulmonary clinic for the first time. Standard clinical data, such as smoking history, body mass index, and age, were collected. Lung function studies conducted in all patients included spirometry, body plethysmography, and airway diffusion, although participat-

ing clinicians were permitted to order additional tests at their own discretion. Clinical diagnoses were separated into 10 predefined disease groups.

The average accuracy of clinicians' diagnoses was 38%. The clinicians were best at identifying chronic obstructive pulmonary disease (COPD), having accurately diagnosed 74% of the cases of this disease. For other disease groups, the clinician's accuracy rarely exceeded 50%. The diagnoses made by AI, on the other hand, on average, were 68% accurate. For diagnosing COPD, the AI achieved a positive predictive value of 83% and a sensitivity of 78%. The positive predictive value and sensitivity of AI for asthma (66% and 82%, respectively) and interstitial lung disease (52% and 59%) were both significantly greater than those achieved by the clinicians.

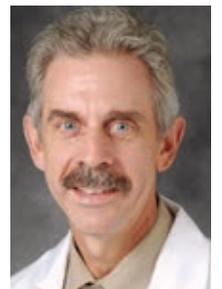
The AI eliminates the potential for a physician's bias to cause one clinical variable to be given more weight relative to another, Dr. Janssens said. Dr. Topalovic and Dr. Janssens reported no relevant financial relationships.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Although most pulmonary physicians are successful at diagnosing

common conditions like COPD and asthma, other diseases of the lungs are more difficult to identify.

The news that the use of artificial intelligence systems may improve diagnostic accuracy is thought provoking. No one expects computer-based systems to replace physicians, but the employment of these systems may benefit patients by leading to more rapid and accurate diagnoses. Testing might therefore be performed in a more parsimonious fashion.



Trials confirm benefits of triple COPD therapy

BY SARA FREEMAN
Frontline Medical News

LONDON – Phase III evidence confirms the multiple benefits of using a triple, fixed-dose combination (FDC) therapy over standard options in patients with severe chronic obstructive pulmonary disease (COPD), according to a presentation on two trials at the annual congress of the European Respiratory Society.

In the TRINITY trial, the combination of the inhaled corticosteroid (ICS) beclometasone dipropionate (BDP), the long-acting beta-agonist (LABA) formoterol fumarate (FF), and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide (GB) delivered via a single pressurized metered-dose inhaler (pMDI), was more effective at reducing exacerbations than was tiotropium bromide (Spiriva, Boehringer Ingelheim) monotherapy.

Results of the TRILOGY trial, which were simultaneously published in *The Lancet* (doi: 10.1016/S0140-6736(16)31354-X) at the time of their presentation at the ERS meeting, showed that the novel single-inhaler, triple fixed-dose combination could induce greater improvements in lung function when compared to a double fixed-dose combination of BDP and FF (Foster, Chiesi Farmaceutici SpA).

“LAMA monotherapy or ICS/LABA are standard options for treating patients with advanced COPD,” Jørgen Vestbo, MD, president of ERS and professor of respiratory medicine at the University of Manchester (England), said in an interview.

Dr. Vestbo, who was an investigator in both the TRINITY and TRILOGY trials, added that the Global



Dr. Jørgen Vestbo

Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines also mention that these drugs can be combined in patients who continue to experience COPD exacerbations. “But the evidence behind that is fairly weak,” he observed.

Although many patients are already being treated with triple therapy, this is via two inhalers, and “there have not been that many really good, long-term outcome studies” that have proven this approach to be the best way to manage those at risk for continued exacerbations of COPD, he said.

Drug companies are now starting to combine these three drugs into one inhaler, however, and this means that registration studies need to be done to get the products licensed, and so “there is an interest in coming up with the evidence,” Dr. Vestbo said.

“What is good about these two studies is that they are both 1-year studies and they are of sufficient size to give quite good estimates ... These are studies that we should have done 5 years ago,” he said. Although the ideal is to have patients on as little therapy as possible, the results of TRINITY and TRILOGY now provide much needed evidence that it will work better than either LAMA or ICS/LABA.

The piece of evidence that is still missing is what the benefit, if any, is over a LAMA/LABA combination, a fact noted during discussion following the presentations of these data at the ERS meeting and in an editorial by Peter Calverley, MD, of the University of Liverpool (England) that accompanied the published TRILOGY findings (*Lancet*. 2016;388:937-8).

There also is a question over whether

twice daily is really better than once daily dosing, or vice versa.

“Until these next studies become available, we can be comforted by the knowledge that three therapies can be combined in a single inhaler which offers more effective therapy than at least one of the recommended treatment regimens for patients with severe COPD,” Dr. Calverley observed in reference to TRILOGY only. He added, “I am not sure that the guidelines [for treating severe COPD] will change much, but at least they can say with better certainty that you can use the triple.”

TRINITY – can triple be better than LAMA monotherapy?

The TRINITY study looked at whether patients with GOLD 3-4 COPD would be better off treated with LAMA monotherapy (tiotropium 18 mcg, one puff per day), the triple fixed-dose combination of BDP (100 mcg), FF (6 mcg), and GB (12.5 mcg) given via the novel pressurized metered-dose inhaler (two puffs twice daily), or a “free” triple combination of BDP (100 mcg) and FF (6 mcg) given via one pressurized metered-dose inhaler (two puffs daily) plus the same dose of the once-daily LAMA.

In all, 2,690 patients were randomized to these three treatments arms. The mean age of patients was 63 years and the majority (74%-77%) were men, with an average FEV₁ predicted of 36% and one COPD exacerbation in the past year. Just under half of the study population were current smokers. Most (75%) had received prior treatment with an ICS/LABA combination, with about 11% receiving LAMA, and the rest either ICS/LAMA (3%), or LABA/LAMA (12%).

The annualized exacerbation rate (the primary endpoint) was 0.457 in the 1,077 patients who were treated with the triple fixed-dose combination versus 0.571 in the 1,074 patients who received tiotropium alone. The rate ratio was 0.8 indicating a 20% reduction in exacerbations was achieved ($P = .003$).

The annualized exacerbation rate in the 532 patients given the “free” triple combination (BDP/FF plus tiotropium) was 0.452, with a rate ratio of 0.790 ($P = .010$) versus those who received the LAMA as monotherapy.

There was no significant difference between the two triple combination strategies.

Presenting these data, Dr. Vestbo

noted that the benefit was seen in preventing both severe and moderate COPD exacerbations. Significantly improved lung function, as measured by the change in FEV₁ from baseline to week 52, was also observed to a greater degree with the triple therapy approaches than with the LAMA monotherapy.

“All three treatments were well tolerated and there were no particular safety concerns in this study,” he said.

TRILOGY – are three drugs better than two?

In contrast to the TRINITY study, the TRILOGY study looked at whether patients with severe COPD would be better off taking an ICS/LABA or the new triple fixed-dose combination pressurized metered-dose inhaler.

Just over 1,200 patients were recruited into the study, which had two co-primary endpoints: change from baseline to week 26 in predose morning FEV₁ and 2-hour postdose FEV₁, and the change in transition dyspnea index focal score at week 26.

Results showed that the triple fixed-dose combination improved predose FEV₁ by 0.081 L and 2-hour postdose FEV₁ by 0.117 L compared with the ICS/LABA combination (P less than .001 for both comparisons). Mean transition dyspnea index scores were 1.71 and 1.50, with a nonsignificant difference of 0.21.

“To be honest, I don’t think we had expected that [the triple combination] would mean much for patients, but we were hoping there would be a significant increase in lung function and a reduction of symptoms,” Dr. Vestbo said about the TRILOGY study. “What we saw was there was [symptomatic improvement] but it was not quite as impressive as we thought, but we reduced exacerbations.”

There was a significant, 23% reduction in the annualized exacerbation rate via the triple combination versus the ICS/LABA combination (0.41 vs 0.53, adjusted rate ratio 0.77, $P = .005$).

The triple approach was well tolerated, with no increase in adverse events versus the dual combination. Chiesi Farmaceutici SpA funded the studies. Dr. Vestbo was an investigator for both TRINITY and TRILOGY and has received honoraria for advising and presenting from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis. Dr. Calverley has consulted for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca.

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The evidence provided from these two trials affirms the treatment strategy employed by many practitioners who treat patients with severe COPD (i.e. using triple therapy). As mentioned in the article, it is not known if this strategy is superior to a LAMA/LABA combination, and if there is any real importance of dosing interval/product selection. In the end, these studies support a prevailing clinical approach and importantly showed a reduction in exacerbation rates.

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Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α -blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the

treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA[®]. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)



The Revatio Family

Available in OS, tablet, and injection forms.

Please see brief summary of Full Prescribing Information on following pages.

Revatio[®]
sildenafil

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4–6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

Incompatibilities Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [see *Warnings and Precautions*], Concomitant use of riociguat, a guanylate cyclase stimulator. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children [see *Use in Specific Populations*].

Hypotension REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Visual Loss When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

Hearing Loss Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Priapism Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

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.

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported by at least 3% of REVATIO-treated patients (20 mg three times a day) and were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates Concomitant use of REVATIO with nitrates in any form is contraindicated [see *Contraindications*].

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis).

Labor and Delivery The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe impairment CL_{Cr} <30 mL/min).

PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only

Rev. June 2015

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Low doses may revive therapy for chronic cough

BY TED BOSWORTH

Frontline Medical News

LONDON – AF-219, a promising targeted therapy for chronic cough derailed by taste disturbances, has been revived by new studies suggesting that there is a therapeutic window that preserves benefits but reduces the risk of the adverse effect, according to new data presented at the annual congress of the European Respiratory Society.

The median duration of chronic



Much lower doses appear to provide near maximum antitussive effects.

cough of the patients on which the new data is based was 13 years. For patients with this type of durable cough history, there is a major unmet need for effective agents, reported Dr. Jacky Smith, MB, ChB, PhD, and professor of respiratory medicine at the University of Manchester (England).

The P2X₃ antagonist AF-219 “is showing real promise as an antitussive agent when used at low doses,” Dr. Smith said.

P2X₃ receptors are expressed by afferent neurons on the vagus nerves and appear to be a strong trigger of cough when stimulated, according to previous work by Dr. Smith and others. AF-219 is an oral antagonist of P2X₃ and produced a 75% reduction in cough frequency when administered in a dose of 600 mg twice daily in a previously reported double-blind, placebo-controlled pilot study (Abdulqawi R et al. *Lancet*. 2015;385:1198-205). “However, there was a small wrinkle. All of the patients had taste disturbances. At this dose, it was primarily loss of taste,” Dr. Smith explained. As P2X₃ is also found on neurons mediating taste, the adverse event was consistent with

the mechanism of AF-219.

A series of studies have since been conducted to show that much lower doses than the twice-daily 600 mg dose employed in the original trial provide an antitussive effect but impose a much reduced risk of affecting taste.

In the latest dose-ranging study, 30 patients, who on average were aged 60 years, were randomized in a crossover design to receive placebo or active therapy in sequential doses over 4 days each of 7.5 mg, 15 mg, 30 mg, or 50 mg twice daily. At the end of the initial 16-day study period and a washout of 14 to 21 days, the patients who were initially randomized to placebo were evaluated on the sequential doses of active therapy, and those previously treated with active therapy took placebo.

On placebo, there was no change in cough frequency. On active therapy, there were incremental reductions in cough at 7.5 and 15 mg, but the differences relative to placebo did not reach statistical significance. Significant reductions in cough frequency relative to placebo were reached on both the 30 mg ($P = 0.001$) and the 50 mg dose ($P = 0.002$). The reductions on these two doses, however, were not significantly different from each other, suggesting that 30 mg may be an adequate dose to achieve clinically relevant antitussive benefits.

Taste disturbances, which were reported in 6.7% of patients taking both the 7.5 mg and 15 mg dose, increased to 46.7% in those taking the 30 mg dose and then to 53.3% of those taking the 50 mg dose. Lack of taste was only reported by 6.7% of those taking the 50 mg dose and none of those taking lower doses.

Other adverse events, such as nasal dryness and rhinitis, were infrequent (less than 10%) and not dose related.

“Significantly lower doses than we originally tested appear to provide near maximum antitussive effects but with a much reduced risk of changes in taste,” Dr. Smith reported.

She added that in this dose-ranging study, there was a correlation between increasing dose and increasing cough-specific measures of quality of life.

“These data support a separation of the dose response relationships for antitussive effects and taste disturbance,” Dr. Smith reported. “Studies of longer duration are needed to test sustained efficacy and tolerability.”

Simtuzumab did not help IPF patients

BY TED BOSWORTH
Frontline Medical News

LONDON – Despite very promising activity in animal models of idiopathic pulmonary fibrosis (IPF), a monoclonal antibody targeted at an enzyme considered to be important to collagen cross-linking did not produce any improvement in progression-free survival (PFS), according to results of a multicenter study presented at the annual congress of the European Respiratory Society.

“This was such a negative study, there is no point in doing another,” reported Ganesh Raghu, MD, FCCP, director of the Pulmonary Fibrosis Program at the University of Washington Medical Center, Seattle.

The focus of this study was simtuzumab, a monoclonal antibody targeted at lysyl oxidase like 2 (LOXL2), an enzyme which catalyzes a step in the formation of collagen crosslinks, which are thought to be important in fibrosis formation. Simtuzumab has been entered into clinical trials for treatment of several forms of fibrosis, including fibrosis in the liver.

“In animal models, simtuzumab has demonstrated efficacy in reducing fibrosis when administered prior to fibrosis formation or after the process has already begun,” Dr. Raghu explained. He said a large trial



DR. RAGHU

was initiated in IPF because the agent seemed so promising and because a large study was thought to be the best strategy to arrive at a definitive answer regarding safety and efficacy.

The drug was found safe but not effective. The independent data monitoring and safety committee terminated the trial early for futility. In the study, 544 IPF patients were randomized to 125 mg simtuzumab or placebo administered subcutaneously once weekly. The primary endpoint was PFS, but there were a large number of secondary endpoints including hospitalization for progressive disease, change in 6-minute

walk distance (6MWD), and overall survival.

For the endpoint of PFS, “there was absolutely no difference” between the groups receiving simtuzumab or placebo. When the patients were stratified for demonstrating above or below median expression of LOXL2, which was a prespecified analysis for the trial, there was still no difference between groups. Even when those in the top quarter percentile of LOXL2 expression were compared with those with less [expression of the enzyme], there was still “absolutely no difference.”

There was also no significant evidence of benefit for simtuzumab observed on key secondary endpoints, such as overall survival. When patients were stratified by baseline lung function as expressed by percentage of predicted forced expiratory volume in 1 second (FEV₁), there was no signal of benefit for those with severe, moderate, or mild impairment.

One criticism of this study raised after the presentation was that patients with 26% or greater of pre-

dicted FEV₁ were permitted into the study. It was suggested that such patients would be expected to already have a high degree of fibrosis and therefore would be less likely to benefit from an antifibrosis therapy. Dr. Raghu acknowledged this criticism, but he said it was important to include patients with advanced disease in order to generate an adequate event rate. Even with inclusion of patients with severe lung impairment, the mortality rate was less than 10%.

He concluded that there was no signal of benefit even among those with the greatest expression of the target.

“We absolutely need better markers for IPF,” Dr. Raghu maintained. While other members of the LOXL family of enzymes may still prove to be valuable markers of IPF risk and targets of therapy, these data appear to rule out a therapeutic role for blocking LOXL2.

Dr. Raghu is a consultant for Boehringer Ingelheim, Biogen, FibroGen, Gilead, Janssen, MedImmune, ProMedior, Sanofi-Aventis, and VeracYTE.

IPF Patient Registry will expand

BY KATIE WAGNER LENNON
Frontline Medical News

The number of patients enrolled in the Idiopathic Pulmonary Fibrosis–Prospective Outcomes (IPF-PRO) Registry will be increased to 1,500, Boehringer Ingelheim Pharmaceuticals and the Duke Clinical Research Institute have announced.

The organizations plan to accomplish this goal by increasing the number of sites they use to gather IPF patient data, according to a statement; the patients enrolled in the registry will now come from 45 sites instead of 18 sites.

IPF-PRO, which was launched in June 2014, is the first multicenter longitudinal disease state registry in the United States focused specifically on IPF. It was designed for the purpose of studying the progression of IPF and the effectiveness of various treatment approaches for the disease. The registry includes a biorepository that stores blood samples that provide patient genetic material.

“In collecting data from a larger, more diverse group of patients ... this registry will allow us to better assess the impact of the disease over time on clinical and patient-centered outcomes,” said Scott M. Palmer, MD, director of pulmonary research at the Duke Clinical Research Institute, Durham, N.C., in the statement.

More information on the registry is available at clinicaltrials.gov/ct2/show/NCT01915511.

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USPSTF: Screen for tuberculosis in those at greatest risk

BY HEIDI SPLETE
Frontline Medical News

Screening for latent tuberculosis infection (LTBI) can help prevent progression to active disease, and the availability of effective tests supports screening asymptomatic adults aged 18 years and older at increased risk for infection, according to new recommendations from the U.S. Preventive Services Task Force.

The recommendations were published online Sept. 6 in JAMA.

“The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons at increased risk for tuberculosis is moderate,” wrote lead author Kirsten Bibbins-Domingo, MD, PhD, of the University of California, San Francisco, and her colleagues (JAMA 2016 Sep 6;316[9]:962-9).

TB infection spreads through the coughing or sneezing of someone with active disease. Individuals at high risk for TB include those who are immunocompromised, residents of long-term care facilities or correctional facilities, or homeless individuals. Those born in countries known to have a high incidence of TB, including China, India, Mexico, and Vietnam, have an elevated risk of getting the infection, compared with people born in countries with low numbers of TB cases.

Other populations at increased risk for TB are contacts of patients with active TB, health care workers, and workers in high-risk settings, the researchers noted.

TB remains a preventable disease in the United States, with a prevalence of approximately 5%, the researchers said.

The two most effective screening tests, tuberculin skin test (TST) and interferon-gamma release assays (IGRA), demonstrated sensitivity and specificity of 79% and 97%, and at least 80% and 95%, respectively.

The recommendations are supported by an evidence review, also published in JAMA (2016 Sep 6;316[9]:970-83). This review included 72 studies and 51,711 adults.

The studies in the evidence review did not assess the benefits vs. harms of TB screening, compared with no screening, noted Leila C. Kahwati, MD, of RTI International in Research Triangle Park, N.C., and her colleagues.

“The applicability of the evidence on accuracy and reliability of screening tests to primary care practice settings and populations is uncertain for several reasons,” the investigators said.

However, the findings suggest that “treatment reduced the risk of active TB among the populations included in this review.”

The researchers reported having no financial conflicts.

Gene mutations predispose to pulmonary fibrosis

BY MARY ANN MOON
Frontline Medical News

Rare frameshift mutations in the NAF1 gene were discovered to cause a telomere-shortening syn-

drome which, among other adverse effects, predisposes carriers to develop pulmonary fibrosis (PF) and emphysema, according to a report published in *Science Translational Medicine*.

“Our findings here ... highlight how telomere shortening is a relevant mechanism for PF-emphysema susceptibility in a subset of patients beyond those with mutations in the telomerase core components. It is

thus possible that efforts to reverse the telomere defect, or other regenerative approaches, will influence the natural history of these progressive pathologies in patients with telo-

Continued on following page

Pertussis often goes undiagnosed

BY ABIGAIL CRUZ
Frontline Medical News

A majority of pertussis cases in the United States may go undetected in people under the age of 50, particularly in adults, results of a retrospective database cohort study suggest.

“The incidence of pertussis in adolescents and adults is very difficult to quantify,” wrote Chi-Chang Chen, MD, of IMS Health, Plymouth Meeting, Pa., and associates, in a study published in *Human Vaccines & Immunotherapeutics* (2016 May; doi: 10.1080/21645515.2016.1186313). Symptoms may be misdiagnosed as other respiratory illnesses, infected individuals may not seek treatment, and pertussis may not be considered as a possible diagnosis in adults, they noted.

To project the possible range of pertussis incidence in this population, the investigator used three different models to analyze information from private insurance and laboratory databases as well as data from the Centers for Disease Control and Prevention for a 6-year period. The first method, which used medical claims for ICD-9 diagnosed pertussis, found an annual incidence rate of 9/100,000 population. The second used a proxy pertussis model that was based on symptoms that could indicate undiagnosed pertussis, showing an incidence rate of 21/100,000. The third method used pathogen data to estimate the fraction of cough illness statistically attributable to pertussis, resulting in an incidence rate of 649/100,000 population, which is 58-93 times higher than the ICD-9 estimated incidence.

These estimates “highlight the need for improved preventive measures – such as increased vaccination – against pertussis,” the investigators said.

The study was funded by GlaxoSmithKline Vaccines.

acruz@frontlinemedcom.com

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}

[‡]The 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.



A reassuring sense of control

Continued from previous page

mere-mediated lung disease,” said Susan E. Stanley, an MD-PhD candidate in the department of oncology, Johns Hopkins University, Baltimore, and her associates.

Pulmonary fibrosis and emphysema cluster in some families, but the

genetic basis of such cases is poorly understood.

Both PF and emphysema have been linked to premature aging of lung tissue and to abnormalities in the maintenance of telomere length. In addition, at least half of patients with familial and sporadic PF, and many with emphysema,

have the clinical features of a short-telomere syndrome, including bone marrow failure/myelodysplastic syndrome, liver disease, and infertility. The diagnosis of a short-telomere syndrome, as opposed to isolated PF-emphysema, is essential for appropriate treatment because if the defect is systemic,

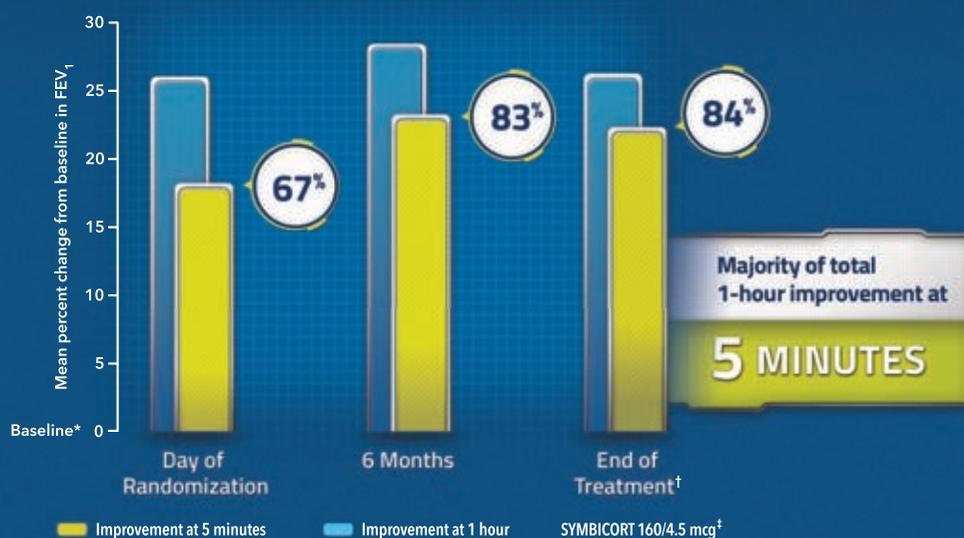
patients will “show exquisite sensitivity to otherwise tolerated medications and procedures, especially in the setting of lung transplantation,” the investigators said (*Sci Transl Med.* 2016;8:351ra107).

To explore the genetic basis of familial PF-emphysema, the researchers performed a series of studies,

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

beginning with whole-genome sequencing on peripheral blood samples from five unrelated probands in familial PF-emphysema pedigrees. These participants had abnormally short telomeres and extrapulmonary features of short-telomere syndrome. Three of them who had low levels of the telomerase RNA component TR

were selected for a candidate gene search, which revealed the NAF1 mutations.

The mutations were found to be present in 2 of 30 (7%) affected members of a prevalence cohort but in none of 134 unaffected control subjects (0%), and in none of 9,006 samples from a public database of

unaffected people (0%). Further genetic laboratory and mouse studies were performed to link the mutations with specific pathologies and to trace their functional effects. Their results led the researchers to conclude that these rare NAF1 variants interfere with RNA biogenesis, causing short telomeres resulting in

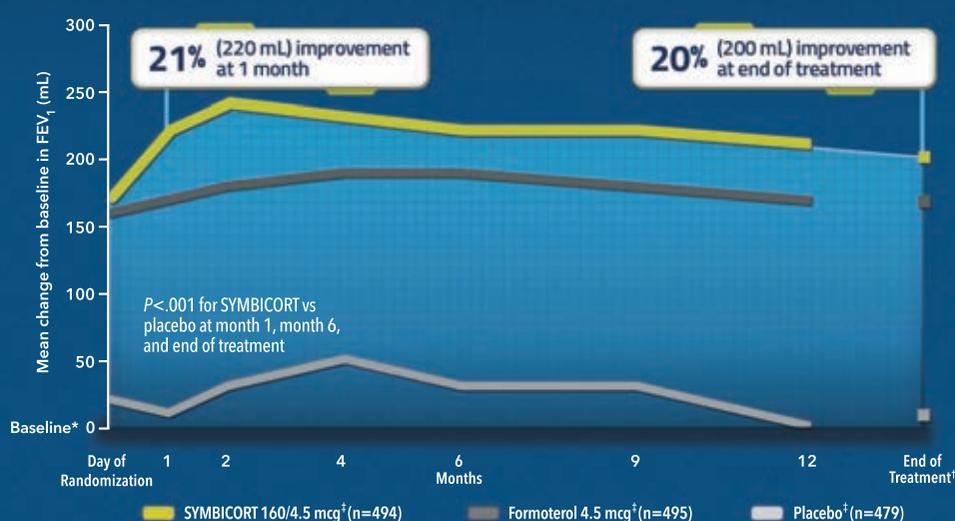
lung disease and other abnormalities.

This work was supported by the National Institutes of Health, the Commonwealth Foundation, and the American Cancer Society.

Ms. Stanley and her associates reported no relevant financial disclosures.

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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Noninvasive ventilation prevents rehospitalization

BY SARA FREEMAN
Frontline Medical News

LONDON – Patients with chronic obstructive pulmonary disease (COPD) and persistent hypercapnia

were half as likely to be readmitted to hospital 1 year after an acute hypercapnic exacerbation if they had received home mechanical ventilation (HMV) in addition to home oxygen therapy (HOT) than if they had not.

The median admission-free survival time in the HOT-HMV U.K. trial was 4.3 months when HMV was used in addition to HOT, versus 1.4 months for HOT alone (unadjusted hazard ratio = 0.54, $P = .007$).

“I think what’s really important is that we now have a treatment that we know that if we direct toward [patients with persistent hypercapnia after acute hypercapnic exacerbation] that we effect a significant change in

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

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 long-acting beta₂-adrenergic agonist (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) in full Prescribing Information].

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 12 years of age and older.

Long-acting beta₂-adrenergic agonists, 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 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 (COPD)

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 approved dosage 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

Long-acting beta₂-adrenergic agonists, 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 prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

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 long-acting beta₂-agonists, 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 long-acting beta₂-agonist (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. Patients should rinse the mouth after inhalation of SYMBICORT.

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 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

their outcomes,” said study investigator Patrick Murphy, MBBS, PhD, a consultant physician and honorary senior lecturer at the Lane Fox Respiratory Unit at Guy’s and St Thomas’ NHS Foundation Trust (London).

Speaking at the annual congress of the European Respiratory Society, he added: “We need to titrate the home

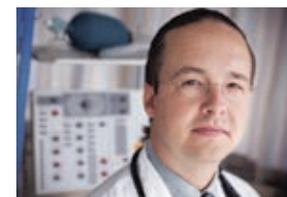
ventilation to control nocturnal hypoventilation, and although I’ve not presented the data as time is short, there is no deleterious effect on quality of life.”

Nicholas Hart, MBBS, PhD, co-study investigator and clinical and academic director of Lane Fox Re-

Continued on following page

VIEW ON THE NEWS

Lee E. Morrow, MD, FCCP, comments: This is a ridiculously common problem that all pulmonologists manage. In an era of pay-for-performance and the dreaded re-admission being foremost in our minds, this is a fascinating and widely applicable article.



SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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[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)*].

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 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, post menopausal 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, 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, bone mineral density 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 (2.1)* and *Use in Specific Populations (8.4)* in 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, 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 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, 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 long-acting beta₂-adrenergic agonist (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 full *Prescribing Information*].

Systemic and inhaled corticosteroid use may result in the following:

- Candida albicans infection [see *Warnings and Precautions (5.4)* in full *Prescribing Information*]
- Pneumonia or lower respiratory tract infections in patients with COPD [see *Warnings and Precautions (5.5)* in full *Prescribing Information*]
- Immunosuppression [see *Warnings and Precautions (5.6)* in full *Prescribing Information*]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions (5.8)* in full *Prescribing Information*]
- Growth effects in pediatric patients [see *Warnings and Precautions (5.14)* in full *Prescribing Information*]
- Glaucoma and cataracts [see *Warnings and Precautions (5.15)* in 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 Patients 12 years 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 mcg taken two 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 two 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 two 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.

Table 1 Adverse reactions occurring at an incidence of ≥ 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 ¹	SYMBICORT		Budesonide	Formoterol	Placebo	
	80/4.5 mcg N = 277	160/4.5 mcg N = 124	80 mcg N = 121	160 mcg N = 109	4.5 mcg N = 237	N = 400
Adverse Event	%	%	%	%	%	%
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

Continued from previous page

spiratory Unit, said in a statement issued by Philips Respironics that the results “have the ability to change the way that COPD patients are treated worldwide.”

“We’re looking forward to continuing the trial over the next 5 years

to monitor survival rates, which we hope will rise, and readmission rates, which will hopefully fall,” he added.

The HOT-HMV UK Trial was conducted in 15 centers and involved patients with severe COPD who had persistent hypercapnia 2-4 weeks after experiencing an acute, life-threatening hypercapnic exacerbation

requiring hospitalization. Persistent hypercapnia was defined as a pH of 7.3 or more and a PaCO₂ of 7 kPa or higher. Patients had to have a 20-year or more pack year history of smoking, a forced expiratory volume in 1 second (FEV₁) of 50% or less, and FEV₁ to forced vital capacity (FVC) ratio of below 60%.

Dr. Murphy observed that the trial design assumed that the rate of hospital readmission at 1 year could be reduced from 55% to 25% with the use of noninvasive ventilation (NIV). The hypothesis was that HMV plus long-term HOT would increase admission-free survival compared with HOT alone.

More than 2,000 patients were initially screened for inclusion in the trial, with 116 randomized. Of the excluded patients, 1,609 did not meet inclusion criteria, 296 declined to participate, and 8 patients were not included for other reasons.

The average age of patients participating in the study was 67 years. The patients had a median body mass index of 21.6 kg/m² and most (61%) were female. Prior long-term oxygen therapy had been used by most (80%), and 61% had three or more

“[We] now have a treatment that we know that if we direct toward [patients with persistent hypercapnia after acute hypercapnic exacerbation] that we effect a significant change in their outcomes ... There is no deleterious effect on quality of life,” Dr. Murphy said.

COPD-related hospital admissions in the last year.

Putting the primary endpoint data into perspective, Dr. Murphy said that six patients with persistent hypercapnia after treatment for an acute exacerbation needed to be treated with HMV to prevent one readmission in the following 12-month period.

Improved nocturnal hypercapnia and sleep-disordered breathing led to improved daytime hypercapnia, he observed. The change in daytime hypercapnia after 6 weeks and 3 months showed a clear statistical benefit for the combined HMV/HOT approach over HOT alone, although this lost statistical significance after 6 and 12 months’ follow-up. “That’s in part explained by the fact that the patient numbers were reduced, but also by the fact that, as part of the trial protocol, once [HOT only] patients had reached the primary outcome we allowed them to move onto HMV.”

Guy’s and St. Thomas’ Charity, Philips Respironics, ResMed, and the ResMed Foundation supported the study. Dr. Murphy has received hospitality for conferences, lecturing, or both from Philips Respironics, Fisher & Paykel Healthcare, and ResMed.

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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Treatment ¹	SYMBICORT		Budesonide		Formoterol		Placebo
	80/4.5 mcg	160/4.5 mcg	80 mcg	160 mcg	4.5 mcg		
Adverse Event	N = 277	N = 124	N = 121	N = 109	N = 237		N = 400
	%	%	%	%	%		%
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 two 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.

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 two 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 ≥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 ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment ¹	SYMBICORT		Budesonide		Formoterol		Placebo
	160/4.5 mcg	160 mcg	4.5 mcg				
Adverse Event	N = 771	N = 275	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 two 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 reported 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 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 asthma patients, 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.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m² basis).

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 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.

In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m² basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis).

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.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m² basis).

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Cytokine shows promise as biomarker for sepsis

BY TED BOSWORTH
Frontline Medical News

LONDON – A cytokine known as tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) is showing potential as a biomarker for evaluating the severity of sepsis and septic shock, according to results of a prospective study presented at the annual congress of the European Respiratory Society.

In a prospective study undertaken in patients administered to an intensive care unit, “lower levels of plasma TRAIL correlated with both organ system dysfunction and mortality,” reported Thomas Nicholson, MD, of Cornell University, New York.

A series of studies associating low levels of TRAIL with increased sepsis severity have attracted attention to this potential biomarker, according to Dr. Nicholson. In a mouse model of sepsis, for example, exogenous administration of TRAIL was associated with improved survival. In a clinical study conducted in CHINA that was cited by Dr. Nicholson, low levels of TRAIL correlated with lower rates of survival.

In the data presented at the ERS

Congress, plasma TRAIL was collected from 108 patients on the first day of ICU admission. Of these patients 59 (54%) had sepsis and 23 (21%) had septic shock. Those with a noninfectious critical illness served as controls.

All patients with sepsis or septic shock were required to meet diagnostic criteria from the recently published Third International Consensus Definitions for Sepsis and Septic Shock (JAMA. 2016;315[8]:801-10). This is important because the newer criteria, relative to previous criteria, have “moved conceptually away from a condition defined by inflammatory biomarkers toward one that emphasizes signs of organ dysfunction,” Dr. Nicholson reported.

Although a dysregulated host response to infection is still a fundamental concept to the newer definition of sepsis, the importance of biomarkers of inflammation has been deemphasized, a change that would not be expected to favor an inflammatory cytokine as a biomarker.

Despite this, plasma TRAIL levels, which were measured with commercially available ELISA kits, were significantly lower for those with sepsis ($P = .038$) and for those with septic shock

(P less than .001) relative to those with a noninfectious critical illness. There was a trend ($P = .077$) for lower plasma levels of TRAIL in patients with septic shock relative to sepsis.

In addition, there was a positive and significant correlation ($r = -0.1983$; $P = .0397$) between plasma TRAIL and degree of organ dysfunction as measured with the Sequential Organ Failure Assessment (SOFA) score. Higher plasma TRAIL levels also predicted survival at 28 days ($P = .016$). Although the overall mortality for patients with sepsis or septic shock in this series was 23%, there were no deaths among sepsis or septic shock patients with a TRAIL above the mean, which was 26.8 pg/mL.

“For every 10 mg/mL increase in TRAIL the odds ratio for survival increased by 1.9-fold,” Dr. Nicholson reported.

TRAIL is implicated in several processes that may explain these observations, according to Dr. Nicholson. For example, he reported that there is evidence that TRAIL induces apoptosis in neutrophils, a suspected mediator of sepsis-related injury.

“The observations in our study are consistent with a growing literature

VIEW ON THE NEWS

Jennifer D. Cox, MD, FCCP,
comments: Biomarkers are an

evolving field that seem to be everywhere. Having a biomarker to help delineate the sepsis/septic shock patient from a noninfectious critical illness patient could be helpful especially when talking to families about severity of illness and possible prognosis. However, ... it should not take the place of clinical judgment.



suggesting that TRAIL is an important mediator of inflammatory cells, such as neutrophils, tempering the degree of inflammation,” Dr. Nicholson explained.

He added that the biomarker is being developed as a potential tool for evaluating sepsis severity.

Dr. Nicholson reported no relevant financial relationships.

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CRITICAL CARE COMMENTARY: Common Canister Policy

BY MARK A. MALESKER,
PHARM D, FCCP

Metered-dose inhalers (MDIs) have been available for more than 50 years and are routinely used. Given the ever-escalating costs of health care, various measures have been targeted by hospitals or health systems to eke out savings. Given the ubiquity of MDIs in the ICU, collaborative efforts, intended to curb rising costs and waste associated with MDI use, have resulted in a variety of protocols generically referred to as common canister policies (CCPs). While the concept of CCPs came into existence in the mid-1990s, casual observation suggests they are gaining momentum at hospitals and long-term care facilities. Most data regarding CCPs come from abstracts or posters; few studies have been published in peer-reviewed journals. Data on the efficacy and safety of CCPs in the ICU are particularly limited. Although most reports on CCPs have originated in community-based hospitals, some academic medical centers have also explored this concept.

What is common canister policy?

CCPs allow a single MDI canister to be shared among patients in a designated care area (typically a ward or ICU), with each individual having his/her own one-way valve holding chamber or spacer (Larson T, et al. *Curr Med Res Opin.* 2015;31[4]:853). Each patient care unit or respiratory therapist has a set of inhalers to use until actuations run out, at which point new inhalers are delivered from the pharmacy. Because the holding chamber or spacer is not shared, the risk of patient-to-patient spread of disease is minimized. In addition, the provider involved in administration of the inhaler must follow a standardized cleaning protocol to ensure the common canister is sterilized after each use.

This policy is designed to be used with inhaled therapies delivered by MDI (albuterol, ipratropium, albuterol/ipratropium, fluticasone, budesonide/formoterol, fluticasone/salmeterol). CCP does not apply to other types of inhalers, such as dry powder or mist inhalers, because the use of a separate holding chamber or spacer is not feasible with these devices. CCP savings are realized through a reduction in the number of MDIs purchased and the ability of patients to be charged per inhalation of medication delivered. An alterna-

tive CCP practice is to issue an MDI to a single patient and, upon his/her discharge, to clean and reissue the patient's partially used MDIs to subsequent patients until the medication is exhausted (Liou J, et al. *Hosp Pharm.* 2014;49:437).

What are the risks and benefits of CCP?

CCP was implemented to minimize costs associated with drug wasting, since patients would not need individual inhalers. Some analysts believe dispensing individual inhalers creates an inherent financial burden as the average length of stay for an acute respiratory hospitalization is 4-5 days (Larson T, et al). Two studies of MDI and dry powder inhaler use in real-world practice found that 11%-13% of the total amount of drug was utilized, leaving 87%-89% of each device wasted at a cost of approximately \$87,000 annually (Larson T,

The decision to enact CCP requires careful analysis, planning, and communication by all key decision makers. State laws must be reviewed for formal statements or regulations regarding CCP.

et al; Sakaan S, et al. *Hosp Pharm.* 2015;50[5]:386).

In addition to cost reductions, one study showed CCP reduced delays in delivery of MDI therapy to patients because the lag time between order entry and delivery of the MDI to the floor was eliminated (Filippelli A, et al. Abstract, ASHP Midyear Clinical Meeting, Dec 1997). In this study, CCP allowed respiratory care practitioners immediate access to the common MDI for their entire shift, creating more efficient delivery of MDI treatments. On a par with findings in prior studies, these investigators observed a 55% reduction in hospital purchase costs for MDIs. Patient-level costs were similarly reduced, as each patient was billed only for the number of doses administered from an MDI, rather than for an entire canister.

While CCPs appear to reduce inhaler-related costs, it is still unclear whether CCP increases the risk of iatrogenic infection. There is a particular paucity of information on the use of CCP in high-risk patients – those with cystic fibrosis,

those in isolation, patients receiving mechanical ventilation, and those who are post transplant or otherwise immunocompromised (Larson T, et al). These patients have an inherently increased risk of developing nosocomial infections including ventilator-acquired pneumonia. A recent prospective study compared MDI CCP with single-patient MDI use in 353 patients supported by mechanical ventilation. Although CCP was associated with cost savings and similar rates of ventilator-acquired pneumonia, hospital mortality, and length of stay, there was a greater frequency of ventilator-associated events among patients in the CCP arm of the study (Gowan M, et al. *Respir Care.* 2016 May 3. pii: respicare.04550. [Epub ahead of print]).

The safety of CCP hinges on proper cleaning of the MDI between users. Typical cleaning protocols include: 1. spraying the MDI mouthpiece with compressed air; 2. cleaning the entire MDI with 70% isopropyl alcohol spray, immersion in isopropyl alcohol for 2 minutes, or cleaning with a bleach swab; and 3. allowing the MDI to air dry before returning it to the shared stock for reissue (Larson T, et al). Although cleaning protocols minimize potential patient harm, they may not always be followed properly. Human errors that put patients at risk for nosocomial infection while utilizing CCP have been reported. In two such instances, patients isolated for methicillin-resistant *Staphylococcus aureus* infection had their individual MDIs put back into the common canister stock and utilized by other patients for approximately 24 hours (Larson T, et al). Once this was noticed, the patients who received inhalations from the "at-risk" MDI were monitored in isolation.

No cross-infection occurred, but the mistake paradoxically increased hospital costs. In another reported instance, a bone marrow transplant patient received MDI therapy from the common canister stock (Larson T, et al). Although no harm occurred, this broke protocol as these patients were excluded from the program because of their increased risk of infection from cross-contamination. Other reports describe protocol breaches such as clinicians not returning MDIs to stock in a timely manner or keeping MDIs in their coat pockets. These events highlight the need for health care professionals associated with CCP to adhere to protocols.

Cross-contamination has been studied at institutions utilizing CCPs. While the majority of reports show no growth in postuse MDI cultures, one study reported growth of group D streptococci when alcohol disinfection did not occur and *Staphylococcus epidermidis* in 5% of the cultures taken after disinfection per protocol (Grissinger M. *P T.* 2013;38[8]:434). Although the bacteria that grew in these studies could be considered environmental contaminants, these findings reinforce the need for concern regarding iatrogenic infection.

The legal landscape

The decision to enact CCP requires careful analysis, planning, and communication by all key decision makers. State laws must be reviewed for formal statements or regulations regarding CCP. Protocol standards should also be evaluated against Joint Commission and Centers for Medicare & Medicaid Services standards for medication administration and storage. Before initiating CCP, communication should occur among risk managers, the pharmacy and therapeutics committee, pulmonologists, respiratory therapists, the medical executive committee, infection control personnel, and the professional liability insurance provider. A contingency plan should be put in place should cross-contamination occur. Note that while the goal of CCP is cost savings, no economic analysis to date has considered the incremental costs of cross-contamination and iatrogenic infection.

What alternative strategies to CCP exist?

CCP aims to turn a single-user multidose inhaler into one that is a unit-dose inhaler shared by multiple patients. One alternative strategy of unit-dose inhalations is nebulization as each treatment consists of a single-use ampule of medication. Another strategy is the use of institutional dose packages that allow hospitals to purchase single-user inhalers limited to five or seven doses of therapy. The prices for nebulized treatments and institutional dose packages may offer cost savings similar to CCP while obviating the increased risk of nosocomial infection.

Dr. Malesker is professor of pharmacy practice and medicine, department of pharmacy practice, School of Pharmacy and Health Professions, Creighton University, Omaha.

Clinical decision tree pinpointed risk

BY AMY KARON
Frontline Medical News

A new classification tool helped guide the treatment of bacteremic patients while clinicians awaited antibiotic resistance results, investigators reported.

The clinical decision tree had a positive predictive value of 91% and a negative predictive value of 92% for determining whether certain gram-negative infections produced extended-spectrum beta-lactamase (ESBL), Catherine Goodman, PhD, of the Johns Hopkins Bloomberg School of Public Health, Baltimore, and her associates wrote online in *Clinical Infectious Diseases*. “These predictions may assist empiric treatment decisions in order to optimize clinical outcomes while reducing administration of overly broad antibiotic agents that can select for further resistance emergence,” they added.

Bacteria that produce ESBL can hydrolyze all broad-spectrum beta-lactam antibiotics except carbapenems. Rapid tests for beta-lactamase genes can shorten the lag time between gram-stain identification and antimicrobial resistance results, but are cost prohib-

itive for most clinical laboratories and often do not assess ESBL gene groups, the researchers said. To find a way to predict which infections are characterized by ESBL production, they studied adults hospitalized at Johns Hopkins from October 2008 to March 2015 with bloodstream isolates of *Klebsiella pneumoniae* (40% of patients), *Klebsiella*

Rapid tests for beta-lactamase genes can shorten the lag time between gram-stain identification and antimicrobial resistance results but are cost prohibitive for most clinical laboratories.

oxytoca (4% of patients), and *Escherichia coli* (56% of patients). Most bacteremias began as urinary tract infections (34% of cases), followed by intra-abdominal infections (24%), catheter-related infections (16%), and biliary infections (14%) (*Clin Infect Dis*. 2016 Jul 26. doi:10.1093/cid/ciw425).

A total of 194 patients (15%) had bacteremias that produced ESBL,

according to the investigators. Using a technique called binary recursive partitioning, they compared these patients with ESBL-negative patients to create a clinical decision tree based on five yes-or-no questions. The tree first asked if the patient had been colonized or infected with ESBL-producing bacteria within 6 months, and if so, whether the patient currently had an indwelling catheter. Patients meeting both criteria had a 92% chance of being ESBL positive. Patients with a recent history of ESBL but no catheter had an 81% chance of being ESBL positive if they were at least 43 years old, but a 75% chance of being ESBL negative if they were under age 43 years.

Among patients with no recent history of ESBL, the decision tree asked about hospitalization in a country with a high ESBL burden and antibiotic therapy during the past 6 months. Patients responding “yes” to both questions had a 100% chance of being ESBL positive. Patients with only the geographic risk factor had a 63% chance of being ESBL negative, and patients with neither risk factor had a 93% chance of being ESBL negative.

VIEW ON THE NEWS

Lee E. Morrow, MD, FCCP, comments: [This study] is remarkably timely as the American Thoracic Society/ Infectious Diseases Society of America pneumonia guidelines were just revised a couple of months ago and they do a pretty big 180 from the prior recommendation of empiric broad-spectrum antibiotics to the current narrow-spectrum therapy regimen with targeted broad-spectrum therapy in high-risk patients. This moves us a step towards knowing who the high-risk patients are.

of ESBL cases because there was a subgroup with no recent ESBL history or geographic exposure, the investigators noted. “The poor predictive nature of health care-associated variables within this patient subset may suggest a high proportion of community-acquired ESBL infections.

The National Institutes of Health funded the study and the researchers reported no conflicts.

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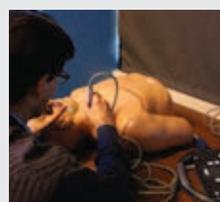
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Smoking thickens LV wall, worsens function

BY MARY ANN MOON
Frontline Medical News

Current smoking, as well as higher levels of cumulative cigarette exposure from past smoking, were both associated with higher left ventricular mass, a higher LV mass-to-volume ratio, and worse diastolic function in an elderly community-based population with no overt indications of coronary artery disease or heart failure, according to a report published online Sept. 13 in *Circulation: Cardiovascular Imaging*.

“These findings suggest that smoking is associated with subtle alterations in LV structure and function, which might help explain the higher risk of heart failure [HF] reported for smokers, independent of coronary artery disease [CAD],” said Wilson Nadruz Jr., MD, of the cardiovascular division, Brigham and Women’s Hospital, Boston, and his associates.

They analyzed links between smoking and echo-

cardiographic features using data from the Atherosclerosis Risk in Communities (ARIC) study, an ongoing prospective observational study involving community-dwelling adults who were aged 45-64 years at baseline in 1987-1989. For their study, Dr. Nadruz and his colleagues assessed echocardiographic images taken for 4,580 ARIC participants at follow-up roughly 25 years later. None of these adults had any indication of CAD or HF; 287 (6.3%) were current smokers, 2,316 (50.5%) were former smokers, and 1,977 (43.2%) never smoked.

Compared with never smokers, current smokers showed a greater LV mass index (80.4 vs. 76.7), a greater LV mass-to-volume ratio (1.93 vs. 1.83), and a higher prevalence of LV hypertrophy (15% vs. 9%), as well as a higher prevalence of concentric LV hypertrophy and worse LV diastolic function. The same association was found between never smokers and former smokers who had higher levels of cumulative cigarette exposure, the investigators said (*Circ Cardiovasc Imag.* 2016 Sep

13. doi: 10.1161/circimaging.116.004950). This association between smoking and altered LV structure and function remained robust after the data were adjusted to account for numerous cardiac risk factors such as older age, higher BMI, diabetes, hypertension, greater alcohol consumption, and higher heart rate. It also didn’t vary by patient sex, race, or income level. In contrast, there was no association between smoking and right ventricular structure or function.

“These data suggest that smoking can independently lead to thickening of the heart and worsening of heart function, which may lead to a higher risk for heart failure, even in people who don’t have heart attacks,” Dr. Nadruz said in a statement.

“The good news is that former smokers had similar heart structure and function, compared with never smokers,” said senior author Scott D. Solomon, MD, professor of medicine at Harvard University, Boston.

Elevated HDL levels predict reduced lung function

BY TED BOSWORTH
Frontline Medical News

LONDON – Having an elevated level of high-density lipoprotein cholesterol (HDL-C) is associated with an

increased rate of lung function decline over time, according to results from a cohort analysis of more than 30,000 adults presented at the annual congress of the European Respiratory Society.

For forced expiratory volume in 1 second (FEV₁), “there was a highly statistically significant inverse association for HDL-C for both cross-sectional and longitudinal measures of lung function,” reported Elizabeth C.

Oelsner, MD, Columbia University Medical Center, New York. Those in the top quartile for HDL-C, on average, had a 9-mL greater decline in FEV₁, compared with patients in the

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lowest quartile (P less than .001). To put this in perspective, Dr. Oelsner said this decline is comparable “to a 10-year increment in pack-years of smoking.”

The study, which pooled six population-based cohorts in the United States, included 31,843 adults for whom there were baseline HDL-C levels and at least two longitudinally collected spirometry readings. Ac-



These data suggest that having an excessively high HDL-C may incur risk just as an excessively low HDL may incur risk.

DR. OELSNER

ording to Dr. Oelsner, quality control criteria were rigorously applied. For example, spirometry measures were obtained according to contemporary standards issued by the American Thoracic Society (ATS).

The average age of the study patients was 57 years, and 45% were classified as never smokers. The mean FEV₁ decline over a median follow-up of 5 years was 37 mL per year (range of 22-49 mL/year across the six cohorts). Approximately 15% of individuals had airflow limitation at baseline. There were more than 300,000 total person-years of observation in the pooled data.

In a fully adjusted cross-sectional analysis, each 1 mmol/L increase (38.67 mg/dL) in HDL-C was associated with a 9-mL lower FEV₁, according to Dr. Oelsner. He said the list of adjusted variables included age, gender, pack-years of smoking, weight, and height.

Results were consistent across age groups, presence or absence of smoking history, body mass index, and the presence or absence of airflow limitations at baseline, according to Dr. Oelsner.

HDL-C's inverse correlation with lung function has been shown in other studies, such as the MESA Lung Study, another population-based analysis, according to Dr. Oelsner. In that study, a 0.4% increase in emphysema on CT lung scans was observed for every 10 mg/dL increase in HDL-C (*Am J Respir Crit Care Med.* 2010;181:A2878).

In this study, “being in the highest quartile for HDL at baseline was associated with an odds ratio of 1.2 for incident airflow limitation relative to being in the lowest [quartile],” Dr. Oelsner said.

The risk of a decline in airway function from an elevated HDL-C, if confirmed, should be considered in the context of the well-known protective effect exerted by HDL against cardiovascular events, according to Dr. Oelsner.

However, she added, these data suggest that “having an excessively

high HDL-C may incur risk just as an excessively low HDL may incur risk.” She noted, “there may be a limitation to the good of the good cholesterol.”

When asked after these data were presented whether she would prefer to have a low or high HDL-C, Dr. Oelsner responded, “Everything in moderation.”

She also advised that studies of treatments designed to raise HDL-C to reduce cardiovascular risk should take lung function into consideration.

The adverse effects of HDL-C on lung function are a potential “off-target risk” from such therapies, Dr. Oelsner warned.

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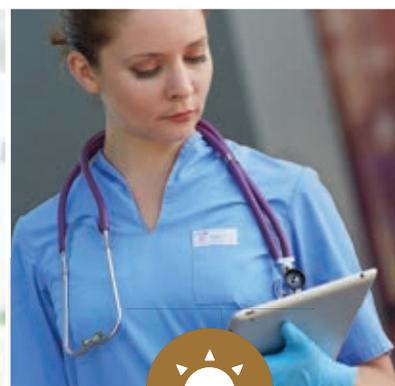
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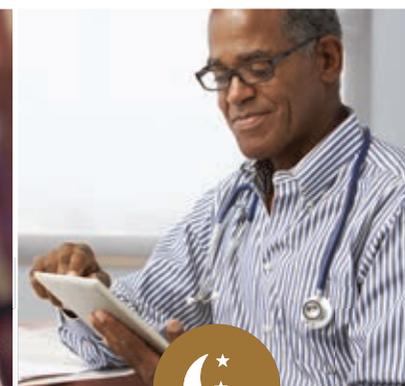
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Rule allows select women to stop anticoagulation

BY BRUCE JANCIN
Frontline Medical News

ROME – Half of all women who experience a first unprovoked venous thromboembolism (VTE) can safely be spared lifelong anticoagulation through application of the newly validated HERDOO2 decision rule, Marc A. Rodger, MD, reported at the annual congress of the European Society of Cardiology.

“We’ve validated that a simple, memorable decision rule on anticoagulation applied at the clinically relevant time point works. And it is



50% of women with unprovoked vein blood clots can be spared the burdens, costs, and risks of lifelong blood thinners.

DR. RODGER

the only clinical decision rule that has now been prospectively validated,” said Dr. Rodger, professor of medicine, chief and chair of the division of hematology, and head of the thrombosis program at the University of Ottawa.

He presented the results of the validation study, known as the REVERSE II study, which included 2,779 patients with a first unprovoked VTE at 44 centers in seven countries. The full name of the decision rule is “Men Continue and HERDOO2,” a name that says it all: the rule posits that all men as well as those women with a HERDOO2 (Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Older age, 2 or more points) score of at least 2 out of a possible 4 points need to stay on anticoagulation indefinitely because their risk of a recurrent VTE off-therapy clearly exceeds that of a bleeding event on-therapy. In contrast, women with a HERDOO2 score of 0 or 1 can safely stop anticoagulation after the standard 3-6 months of acute short-term therapy.

“Sorry, gentlemen, but we could find no low-risk group of men. They were all high risk,” he said. “But 50% of women with unprovoked vein blood clots can be spared the burdens, costs, and risks of lifelong blood thinners.”

Dr. Rodger and colleagues began developing a multivariate clinical decision rule in 2001. They examined 69 risk predictors, which they winnowed down to four potent risk

predictors identified by the acronym HERDOO2.

The derivation study was published 8 years ago (CMAJ. 2008;Aug 26;179[5]:417-26). It showed that women with a HERDOO2 score of 2 or more as well as all men had roughly a 14% rate of recurrent VTE in the first year after stopping anticoagulation, while women with a score of 0 or 1 had about a 1.6% risk. The International Society

on Thrombosis and Haemostasis suggests that it’s safe to discontinue anticoagulants if the risk of recurrent thrombosis at 1 year off-therapy is less than 5%, given the significant risk of serious bleeding on-therapy and the fact that a serious bleed event is two to three times more likely than a VTE to be fatal.

The researchers recognized that a clinical decision rule needs to be externally validated before it’s ready for prime-time use in clinical practice. Thus, they conducted the REVERSE II study, in which the decision rule was applied after the 2,799 participants had been on anticoagulation for 5-12 months. All had a first proximal deep vein thrombosis and/or a segmental or greater pulmonary embolism. Patients were still on anticoagulation at the time the rule was applied, which is why the cut point for a positive D-dimer test in HERDOO2 is 250 mcg/L, half of the threshold value for a positive test in patients not on anticoagulation.

They identified 631 women as low risk, with a HERDOO2 score of 0 or 1. They and their physicians were instructed to stop anticoagulation at that time. The 2,148 high-risk subjects – that is, all of the men and the high-risk women – were advised to remain on anticoagulation. The primary study endpoint was the rate of recurrent VTE in the 12 months following testing and patient guidance. The lost-to-follow-up rate was 2.2%.

The recurrent VTE rate was 3% in the 591 low-risk women who discontinued anticoagulants and zero in 31 others who elected to stay on medication. In the high-risk group identified by the HERDOO2 rule, the recurrent VTE rate at 12 months was 8.1% in the 323 who opted to discontinue anticoagulants and just 1.6% in 1,802 who continued on therapy as advised, a finding that underscores the effectiveness of selectively applied long-term anticoagulation therapy.

Scoring using the HERDOO2 rule

Risk predictor	Value
H Hyperpigmentation,	1 point
E Edema, or	1 point
R Redness in either leg	1 point
D D-dimer test positive at 250 mcg/L or more	1 point
O Obesity, with a BMI of 30 kg/m ² or more	1 point
O Older age (65 years or greater)	1 point
2	2 or more points place a woman at high risk of recurrent VTE if she is off anticoagulant therapy

Note: The REVERSE II validation study involved 2,779 patients with a first unprovoked venous thromboembolism.

Source: Dr. Rodger

The recurrent VTE rate among the 291 women with a HERDOO2 score of 0 or 1 who were on exogenous estrogen was 1.4%, while in high-risk women taking estrogen the rate was more than doubled at 3.1%. But in women aged 50-64 identified by the HERDOO2 rule as being low risk, the actual recurrent VTE rate was 5.7%, a finding that raised a red flag for the investigators.

“There may be an evolution of the HERDOO2 decision rule to a lower age cut point. But that’s something that requires further study in postmenopausal women,” he said.

An unprovoked index venous thromboembolism was defined as occurring in the absence of the following conditions: a leg fracture or lower-extremity plaster cast, immobilization for greater than 3 days, surgery using a general anesthetic in the 3 months before the index event, and a diagnosis of a malignant disease in the past 5 years.

Venous thromboembolism is the second most common cardiovascular disorder and the third most common cause of cardiovascular death. Unprovoked VTEs account for half of all VTEs. Their management has been a controversial subject. Both the American College of Chest Physicians and the European Society of Cardiology recommend continuing anticoagulation indefinitely in patients who aren’t at high bleeding risk.

“But this is a relatively weak 2B recommendation because of the tightly balanced competing risks of recurrent thrombosis off anticoagulation and major bleeding on anticoagulation,” Dr. Rodger said.

He added that he considers REVERSE II to be practice changing, and predicted that once the results are published the guidelines will be revised.

Discussant Giancarlo Agnelli, MD, was a tough critic who gave fair warning.

“I am friends with many of the authors of this paper, and in this country we are usually gentle with enemies and nasty with friends,” declared Dr. Agnelli, professor of internal medicine and director of internal and cardiovascular medicine and the stroke unit at the University of Perugia, Italy.

He didn’t find the REVERSE II study or the HERDOO2 rule persuasive. On the plus side, he said, the HERDOO2 rule has now been validated, unlike the proposed

DASH and Vienna rules. And it was tested in a diverse multinational patient population. But the fact that the HERDOO2 rule is only applicable in women is a major limitation. And REVERSE II was not a randomized trial, Dr. Agnelli noted.

Moreover, 1 year of follow-up seems insufficient, he continued. He cited a French multicenter trial in which patients with a first unprovoked VTE received 6 months of anticoagulants and were then randomized to another 18 months of anticoagulation or placebo.

During that 18 months, the group on anticoagulants had a significantly lower rate of the composite endpoint comprised of recurrent VTE or major bleeding, but once that period was over they experienced catchup. By the time the study ended at 42 months, the two study arms didn’t differ significantly in the composite endpoint (JAMA. 2015 Jul 7;314[1]:31-40).

More broadly, Dr. Agnelli, the lead investigator in the AMPLIFY study, also questioned the need for an anticoagulation discontinuation rule in the contemporary era of new oral anticoagulants (NOACs). “Why should we think about withholding anticoagulation ... when we now have such a safe approach?” he asked. AMPLIFY was a randomized trial of fixed-dose apixaban (Eliquis) versus conventional therapy with subcutaneous enoxaparin (Lovenox) bridging to warfarin in 5,395 patients with acute VTE. The NOAC was associated with a 69% reduction in the relative risk of bleeding (N Engl J Med. 2013 Aug 29;369[9]:799-808).

Dr. Rodger reported receiving research grants from the French government and Biomerieux, which funded the REVERSE II study. Dr. Agnelli reported having no financial conflicts.

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NETWORKS: Therapeutic bronchoscopy, PETCO₂, Estrogen in PAH

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Central airway obstruction (CAO) is a major cause of morbidity and mortality in patients with malignant and nonmalignant pulmonary disorders (Ernst et al. *Am J Respir Crit Care Med*. 2004;169[12]:1278). It is associated with postobstructive pneumonia, respiratory compromise, and even respiratory failure. It often precludes the patients with malignancy from getting definitive treatment, such as surgical resection or chemotherapy. Therapeutic bronchoscopy using a rigid bronchoscope plays a central role in managing these patients.

Different modalities used during therapeutic bronchoscopy include debridement, airway dilation, and different heat therapies, such as laser,

electrocautery, and argon plasma coagulation (Bolliger et al. *Eur Respir J*. 2006;27[6]:1258). Airway stents are often placed to achieve durable airway patency. Endobronchial therapies with delayed effect include brachytherapy, photodynamic therapy, and cryotherapy (Vergnon et al. *Eur Respir J*. 2006;28[1]:200). There is improvement in symptom control, quality of life, and spirometry with successful bronchoscopic intervention (Mahmood et al. *Respiration*. 2015;89[5]:404). Patients with respiratory failure secondary to CAO can be weaned from mechanical ventilation (Murgu et al. *Respiration*. 2012;84[1]:55).

It is often difficult to predict which patients will have a successful bronchoscopic intervention. Endobronchial disease and stent placement have been associated with successful outcome (Ost et al. *Chest*. 2015;147[5]:1282). Patients with unsuccessful bronchoscopic intervention often have a poor prognosis, despite concurrent chemotherapy and radiation (Mahmood et al. *Respiration*. 2015;89[5]:404).

As more fellowship programs are offering training in rigid bronchoscopy, there is a need to standardize the training and use validated tools to

assess competency. RIGID-TASC (Rigid bronchoscopy Tool for Assessment of Skills and Competence) is one such tool, which can be utilized for this purpose to provide objective feedback to the trainee (Mahmood et al. *Ann Am Thor Soc*. 2016. doi: 10.1513/ Epub ahead of print).

Kamran Mahmood, MD, MPH, FCCP
Steering Committee Member



DR. MAHMOOD

Pediatric Chest Medicine

CHEST Foundation campaign to fight difficult-to-control asthma

The CHEST Foundation and the Asthma and Allergy Network have joined forces to combat difficult-to-control asthma with the campaign "Asthma: Take Action. Take Control." Affecting approximately 235 million people worldwide, asthma morbidity continues to have a significant impact on quality of life for both children and adults with asthma. In the United States alone, it accounts for health-care costs of approximately 60 billion dollars.

The campaign educates patients, caregivers, families, and health-care providers about current

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DR. CATALETTO

treatment options for asthma, highlights the importance of specialist referrals, and encourages patients to participate with their health-care provider to achieve asthma control. Because asthma may fall into this difficult-to-control category for many reasons, including poor adherence, unresponsiveness to conventional therapies,

failure to recognize and manage triggers, and co-morbidities, this campaign developed materials to improve health literacy so that patients can take an active and informed role in asthma self-management. Written in an easy to understand format and language, the “Take Control” campaign highlights four key steps:

- Tell your doctor when it’s hard to breathe.
- Ask your doctor for an asthma action plan.
- Practice your asthma action plan.
- Know that asthma shouldn’t hold you back.

Newly developed materials include tips and resources for children and adults to learn about asthma and raise awareness about difficult-to-control asthma. These materials can be found at asthma.chestnet.org.

Mary Cataletto MD, FCCP
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Current clinical usefulness of the PETCO_2 during exercise testing

Dynamic measurement of the PETCO_2 in cardiopulmonary exercise testing may demonstrate unique changes throughout exercise in specific diseases and is often underutilized during interpretation.



DR. CHAABAN

Though it can be affected by hyperventilation and the VD/VT relationship, normally it rises from rest to lactate threshold (LT), then declines from peak exercise through recovery (Ramos RP, et al. *Pulm Med*. 2013;2013:359021. doi: 10.1155/2013/359021.) In severe pulmonary hypertension and shunts, the reverse occurs, declining in early exercise and then rising during recovery (Sun XG, et al. *Circulation*. 2002;105[1]:54). Blunting or reversal of this exercise decline in PETCO_2 has been correlated with clinical improvement in therapeutic trials (Oudiz RJ, et al. *Eur J Heart Fail*. 2007;9[9]:917).

Studies in severe CHF have correlated prognosis with lower values at rest and greater decline from rest to peak exercise, the latter being affected by adequacy of effort and assessed by RQ. They, however, do not take into account the normal rise and fall before and after LT (Arena R, et al. *Am Heart J*. 2008;156[5]:982) (Hoshimoto-Iwamoto M, et al. *J Physiol Sci*. 2009;59[1]:49). In pulmonary hypertension, as the disease progresses, the unique reversal of the normal slopes of the PETCO_2 that occurs, negative in early exercise and positive during re-

covery in association with an excessive alveolar ventilator response, needs further clinical investigation and correlation (Yasunobu Y, et al. *Chest*. 2005;127[5]:1637). The dynamic changes that occur in the PETCO_2 throughout exercise may be an additional tool to use in selective conditions to more accurately assess prognosis and monitor response to therapy.

Said Chaaban, MD; and Zachary Morris, MD, FCCP
Steering Committee Members

Pulmonary Vascular Disease

Estrogen in PAH: Is it good or bad?

The role of sex hormones in the development and perpetuation of pulmonary arterial hypertension (PAH) continues to be an open field of active research. Epidemiology reveals that PAH is more prevalent in women in both idiopathic and heritable cases.¹ On the other hand, data demonstrate that prognosis of PAH in men is worse than in women and, in animal research, estrogens provide a protective effect. This constitutes the “estrogen paradox.” Estrogen plays a protective role in the vasculature, modulating proliferative and vasoactive signaling by direct and receptor-mediated mechanisms.^{2,3} In animal models of PAH, estrogen increases nitric oxide and prostacyclin production and decreases endothelin-1, resulting in beneficial vascular effects.⁴ However, the Women’s Health Initiative revealed that hormone replacement therapy increases the risk for adverse cardiovascular events.⁵ In familial PAH, estrogen is a potent mitogen of pulmonary vascular smooth muscle cells.⁶ A recently published study, first in humans, by Ventetuolo et al.⁷ showed higher levels of estrogen (E2) and lower level of dehydroepiandrosterone-sulfate (DHEAS) in men with PAH, compared with normal men without cardiovascular disease (MESA study), supporting the role of the estrogen pathway in the development of PAH. Experimental data implicate estrogens as promoters of vascular proliferation and cell damage but also as inhibitors of pulmonary vasoreactivity. In vitro, estrogen is mitogenic and promotes proliferation of pulmonary vascular smooth muscle cells.⁶ Despite advances, the role of sex and estrogen in PAH is not fully understood. More preclinical and clinical data are necessary to establish a potential role for estrogen-based therapies in this disease.

Sandeep Sahay, MD; and Hector R Cajigas, MD
Steering Committee Members

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Thoracic Oncology

The “new” lung cancer staging system

Definition of lung cancer stage is an essential part of defining prognosis, developing treatment plans, and conducting and reporting on clinical research studies.



DR. VACHANI

The stage classification system is determined by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC). The 7th edition of the lung cancer staging system, published in 2009, was a landmark effort based on a large multicenter international

database created by the Staging and Prognostic Factors (SPFC) of the International Association for the Study of Lung Cancer (IASLC) and backed by careful validation and statistical analysis.

The IASLC Lung Cancer Staging Committee has been working on the 8th edition of the TNM classification for lung cancer. The database used for analysis consists of 94,708 patients diagnosed between 1999 and 2010, and included cases from 35 sources and 16 countries. Multiple analyses were performed to assess the ability of T, N, and M descriptors to predict prognosis and to identify new cutpoints for inclusion in the eighth edition.¹⁻³ The proposed changes include new cutpoints for the T component based on 1-cm increments, new categories for the N component, a new M category to specifically identify patients with oligometastatic disease, and multiple updates to the overall TNM stage groupings.⁴ In addition, the proposal includes recommendations for coding T stage for subsolid nodules and assessment of tumor size in part-solid nodules.⁵ These proposed changes will be submitted to the UICC and AJCC for inclusion in the eighth edition and will be enacted in January 2017.

Anil Vachani, MD, FCCP
NetWork Vice-Chair

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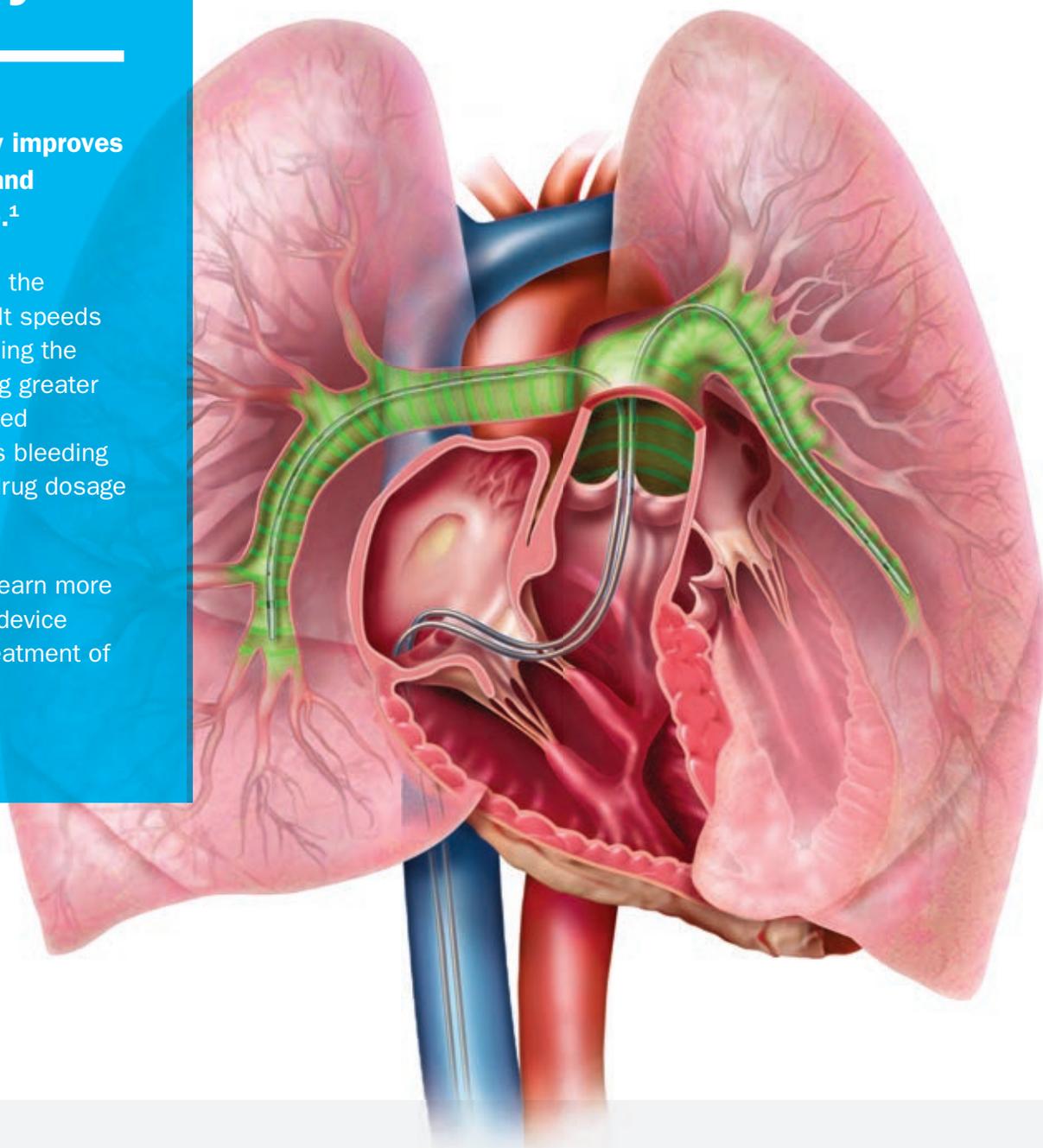
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² Braaten, J et al., *Thromb Haemost* 1997;78:1063-8; Francis, C et al. *Ultrasound in Medicine and Biology* 1995; 21(3):419-424; Soltani, A et al., *Physics in Medicine and Biology* 2008; 53:6837-6847

³ Kucher, N., et al., *Circulation*, Vol. 129, No. 4, 2014, 479-486.

⁴ Piazza, G., et al., *American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

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