



CHEST[®] Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY DR. NAIR

Dr. Parameswaran Nair: "Long-term use of systemic corticosteroids can lead to potentially life-threatening complications."

Biologic cut steroid dose in severe asthma

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – The biologic benralizumab cut glucocorticoid dosage by nearly 75% among patients with severe, uncontrolled asthma, compared with a 25% reduction in dosage among patients using a placebo, a study showed.

In this three-armed, double-blind study of 220 patients, those administered benralizumab every 4 and 8 weeks were 4.09 (95% confidence interval, 2.22-7.57) and 4.12 (95% CI, 2.22-7.57) times as likely to see a reduc-

tion in glucocorticoid dose, compared with those in the placebo group, the investigators reported (N Engl J Med. 2017 May 21. doi: 10.1056/NEJMoa1703501). The study was presented at an international conference of the American Thoracic Society and published simultaneously in the New England Journal of Medicine.

The results of this phase III trial could be significant for patients with severe asthma who must choose between passing on treatment and facing the potential risks associated with glucocorticoid use. See **Biologic** • page 4

Imatinib cuts mast cells, reduces airway response

Studied in adults with severe asthma.

BY MARY ANN MOON
Frontline Medical News

Imatinib decreased airway mast-cell counts and airway hyperresponsiveness in adults with asthma, who were not responding well to maximal therapy, according to a report published online May 17 in the New England Journal of Medicine.

Imatinib is an inhibitor of the stem-cell factor receptor KIT, which is essential for mast-cell development and survival in bodily tissues. This study's findings suggest that KIT-dependent processes and mast cells contribute to the pathobiology of severe asthma.

"These data are not clinically directive, but they set the stage for follow-up studies targeting mast cells," said Katherine N. Cahill, MD, of Brigham and Women's Hospital and Harvard Medical School, both in Boston, and her associates.

The researchers undertook this study because imatinib is known to reduce bone-marrow mast cells and tryptase levels in chronic myeloid leukemia and to reduce serum tryptase in patients with pulmonary hypertension. Tryptase is a marker of mast-cell burden and activation when detected in extracellular fluids,

See **Imatinib** • page 7

MK-7264 reduced chronic cough frequency in phase II study

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – A new oral drug that blocks a nerve ion channel was generally tolerable and effective at reducing chronic, refractory cough in a placebo-controlled,

dose-ranging, phase II study with 252 patients.

A 50-mg b.i.d dosage of MK-7264 cut cough frequency by at least 30% in 80% of patients, compared with 44% of patients on placebo, Jaclyn A. Smith, MD, said at an international conference of the Amer-

ican Thoracic Society.

At that dosage, 48% of patients reported some change in their taste sensations, an expected drug effect, with about 40% characterizing it as very bothersome or extremely bothersome. An additional 9% reported a

See **Chronic cough** • page 13

INSIDE

Lung Cancer NSCLC

EBUS-TBNA appears cost effective for staging in some circumstances. • 8

Sleep Medicine OSA

Diagnoses made less often in women. • 12

Pulmonary Medicine Sarcoidosis

Disease is worse in blacks than whites. • 14

Cardiothoracic Surgery

Mitral valve replacement

Percutaneous method unlikely to become standard of care. • 19

News From CHEST Pulmonary Perspectives[®]

China's crisis. • 36

COMING SOON

A new look for



THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct., KY

CHANGE SERVICE REQUESTED

CHEST PHYSICIAN
151 Fairchild Ave.,
Suite 2,
Plainville, NY 11803-1709

HELP PRESERVE MORE LUNG FUNCTION

Reduce lung function decline with Esbriet¹⁻⁴

BROAD PATIENT POPULATION



Clinical trials included patients with IPF with a range of clinical characteristics, demographics, and select comorbidities^{1*}

DEMONSTRATED EFFICACY



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

IPF=idiopathic pulmonary fibrosis.

*Baseline characteristics (including clinical characteristics, demographics, and select comorbidities) were well balanced across treatment groups, with 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624).^{1,2}

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

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

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

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

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

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

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Genentech

A Member of the Roche Group

**NOW APPROVED
in Tablets**

**ESTABLISHED
SAFETY AND
TOLERABILITY**



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

**COMMITTED
TO PATIENTS**



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

**WORLDWIDE
PATIENT
EXPERIENCE**



More than 31,000 patients have taken pirfenidone worldwide^{1,2||}

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

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

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

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

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

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

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

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

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

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

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

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

Esbriet
(pirfenidone) tablets 267 mg
801 mg

Some ceased glucocorticoid use

Biologic from page 1

“Frequent or long-term use of systemic corticosteroids can lead to potentially life-threatening complications, including osteoporosis, diabetes, cardiovascular disease, and

adrenal suppression,” Parameswaran Nair, MD, PhD, professor of medicine at McMaster University, Hamilton, Ont., said in a press release. “We need new, safe therapies that would

replace the need for systemic corticosteroids for patients with severe asthma.”

To test benralizumab’s effectiveness, the investigators measured a baseline level of glucocorticoid dosage of 220 patients with severe, uncontrolled asthma. Patients were then given one of three treatment

options: one dose of benralizumab every 4 weeks, one dose of benralizumab every 8 weeks, or a placebo. All three treatments were decreased each time until minimal dosage was found while still maintaining asthma control.

The average age of patients was approximately 50 years; the majority of

Esbriet
(pirfenidone) tablets

Rx only

BRIEF SUMMARY

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

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

5.2 Photosensitivity Reaction or Rash

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

5.3 Gastrointestinal Disorders

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

ESBRIET® (pirfenidone)

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

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

Strong CYP1A2 Inhibitors

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

patients in both treatment groups and the placebo group were female.

The researchers also analyzed patients' accounts of any worsening asthma symptoms, which were recorded in an electronic asthma daily diary.

Along with the median 75% decrease in glucocorticoid dosage seen

in both groups of patients receiving benralizumab, 24 patients (33%) in the 4-week group and 27 patients (37%) in the 8-week group showed a 90% reduction from their baseline glucocorticoid dosage. In contrast, only nine patients (12%) in the placebo group experienced a 90% drop in glucocorticoid use.

The researchers also found benralizumab might be useful in a subgroup of patients with a baseline prednisone dose of less than 12.5 mg. These patients were more likely to stop taking their glucocorticoid dose if they were taking benralizumab instead of the placebo. Specifically, patients who took

ESBRIET® (pirfenidone)

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

Moderate CYP1A2 Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

7.2 CYP1A2 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

ESBRIET® (pirfenidone)

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

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

8.7 Renal Impairment

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

8.8 Smokers

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

10 OVERDOSAGE

There is limited clinical experience with 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.

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way, South San Francisco, CA 94080-4990

Genentech

A Member of the Roche Group

ESBRIET® is a registered U.S. trademark of Genentech, Inc.
© 2017 Genentech, Inc. All rights reserved. ESB/100115/0470(2) 2/17



Dr. Parameswaran Nair speaks during a session at the ATS.

benralizumab every 4 weeks were 5.23 times more likely, and those who took the biologic every 8 weeks were 4.19 times more likely, to cease using glucocorticoids.

Similar to the current biologics used to treat severe eosinophilic asthma, mepolizumab and reslizumab, benralizumab is a form of a monoclonal antibody. Instead of targeting interleukin-5, benralizumab works against a subunit of the interleukin-5 receptor. The investigators said this aspect of benralizumab may explain why it was successful in this study.

“Targeting of the alpha subunit of the interleukin-5 receptor with benralizumab has potential advantages over existing anti-interleukin-5 therapies,” Dr. Nair said. “By targeting the interleukin receptor rather than the cytokine, luminal depletion of eosinophils can occur, which may be related to greater clinical efficiency.”

The investigators noted that forced expiratory volume in 1 second levels seemed relatively unaffected by benralizumab.

This study was limited by the length of the trials, which lasted 28 weeks. Investigators also noted that 20% of the original patients were not used in the final population.

This study was sponsored by, and organized in partnership with, AstraZeneca. All of the investigators reported receiving personal fees, grants, or other support from AstraZeneca, or being under contract with the company. Most of the authors also reported relationships with other pharmaceutical companies.

Mepolizumab boosts remission in EGPA

Eosinophilic granulomatosis with polyangiitis went into remission for 24 weeks in 28% of those treated.

BY MARY ANN MOON
Frontline Medical News

Adding mepolizumab to standard-of-care glucocorticoids with or without immunosuppressive agents can induce remission in many patients who have eosinophilic granulomatosis with polyangiitis (EGPA), according to a report published online May 18 in the *New England Journal of Medicine*.

EGPA, a rare disorder characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and eosinophilic vasculitis in at least one end-organ, frequently relapses de-

spite glucocorticoid therapy or fails to respond adequately to the treatment. Patients have elevated levels of the cytokine interleukin-5, which regulates eosinophil maturation, differentiation, and proliferation. Neutralizing this cytokine is thought to be a potential therapeutic approach, said Michael E. Wechsler, MD, of National Jewish Health, Denver, and his associates.

Proof-of-concept studies have demonstrated the efficacy of subcutaneous mepolizumab, an anti-interleukin-5 monoclonal antibody, in EGPA, so Dr. Wechsler and his colleagues assessed the safety and

efficacy of a 1-year course of mepolizumab (300 mg) as add-on therapy in a double-blind, randomized, phase III trial, which involved 136 adults treated at 31 academic medical centers in nine countries. The study was

in remission for a full year (19% vs. 1%; OR, 19.65). The time to first relapse was significantly longer for mepolizumab, with only 56% of that group experiencing a relapse within 1 year, compared with 82% of the placebo group.

Significantly more patients in the mepolizumab group (32%) than in the placebo group (3%) were in remission at both week 36 and week 48 (odds ratio, 16.74).

sponsored by GlaxoSmithKline and the National Institute of Allergy and Infectious Diseases.

The first of two primary efficacy endpoints was the total accrued weeks of remission. A total of 28% of the mepolizumab group achieved remission for at least 24 weeks, compared with only 3% of the placebo group, for an odds ratio of 5.91.

The second primary efficacy endpoint was the proportion of patients in remission at both week 36 and week 48. Again, significantly more patients in the mepolizumab group (32%) than in the placebo group (3%) met this endpoint (OR, 16.74).

Mepolizumab also proved superior to placebo regarding numerous secondary endpoints, the investigators said (*N Engl J Med*. 2017 May 18. doi: 10.1056/NEJMoa1702079). More patients who received active treatment achieved remission within the first 6 months of treatment and remained

in remission for a full year (19% vs. 1%; OR, 19.65). The time to first relapse was significantly longer for mepolizumab, with only 56% of that group experiencing a relapse within 1 year, compared with 82% of the placebo group.

The annualized relapse rate was half as high with mepolizumab (1.14) as with placebo (2.27). In addition, patients in the mepolizumab group were more likely to reduce their doses of glucocorticoids (OR, 0.20) or discontinue the drugs altogether (18% vs. 3% taking placebo).

Mepolizumab was most effective among the 79 patients who had a high absolute eosinophil count (150 or more cells per cubic millimeter) at baseline. In this subgroup, 33% of patients taking mepolizumab achieved remission for 6 months or more, compared with none of the patients taking placebo (OR, 26.1).

Although the effectiveness of mepolizumab in this difficult-to-treat population was noteworthy, only about half of the patients given the active treatment achieved remission as defined by the study protocol. It is unclear why the drug was not effective in

Continued on following page

IN THIS ISSUE

News From CHEST • 24

CHEST Foundation

Foundation collaborates with various organizations. • 25

CHEST Physician Is Online

CHEST Physician is available on the Web at chestphysician.org



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

CHEST[®] Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

AMERICAN COLLEGE OF CHEST PHYSICIANS (CHEST)

Editor in Chief Vera A. De Palo, MD, MBA, FCCP
Deputy Editor in Chief David A. Schulman, MD, FCCP
President Gerard A. Silvestri, MD, MS, FCCP
Executive Vice President & CEO Stephen J. Welch
Manager, Editorial Resources Pamela L. Goorsky
Pubs & Digital Content Editor Martha Zaborowski
Section Editors
Nitin Puri, MD, FCCP - **Pulmonary Perspectives**
Lee E. Morrow, MD, FCCP - **Critical Care Commentary**
Jeremy A. Weingarten, MD, FCCP - **Sleep Strategies**

EDITORIAL ADVISORY BOARD

G. Hossein Almassi, MD, FCCP, Wisconsin
Jennifer Cox, MD, FCCP, Florida
Jacques-Pierre Fontaine, MD, FCCP, Florida
Eric Gartman, MD, FCCP, Rhode Island
Octavian C. Ioachimescu, MD, PhD, FCCP, Georgia
Jason Lazar, MD, FCCP, New York
Susan Millard, MD, FCCP, Michigan
Michael E. Nelson, MD, FCCP, Kansas
Daniel Ouellette, MD, FCCP, Michigan
Frank Podbielski, MD, FCCP, Massachusetts
M. Patricia Rivera, MD, FCCP, North Carolina
Nirmal S. Sharma, MD, Alabama
Eleanor Summerhill, MD, FCCP, Rhode Island
Krishna Sundar, MD, FCCP, Utah

E-mail: chestphysiciannews@chestnet.org

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for CHEST PHYSICIAN is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.

The statements and opinions expressed in CHEST PHYSICIAN do not necessarily reflect those of the American College of Chest Physicians, or of its officers, regents, members, and employees, or those of the Publisher. The American College of Chest Physicians, its officers, regents, members, and employees, and Frontline Medical Communications Inc. do not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to products, drugs, or services mentioned herein.

POSTMASTER: Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Service, 151 Fairchild Ave., Suite 2, Plainville, NY 11803-1709.

CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is \$237.00 per year. Phone 973-206-3434, fax 973-206-9378.

EDITORIAL OFFICES 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

ADVERTISING OFFICES 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

©Copyright 2017, by the American College of Chest Physicians

FRONTLINE MEDICAL COMMUNICATIONS SOCIETY PARTNERS

VP/Group Publisher, Director, FMC Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Creative Director Louise A. Koenig
Director, Production/Manufacturing Rebecca Slebodnik
Director, Business Development Angela Labrozzi, 973-206-8971, cell 917-455-6071, alabrozzi@frontlinemedcom.com
Classified Sales Representative Drew Endy 215-657-2319, cell 267-481-0133 dendy@frontlinemedcom.com
Senior Director of Classified Sales Tim LaPella, 484-921-5001, tlapella@frontlinemedcom.com



FRONTLINE MEDICAL COMMUNICATIONS

Chairman Stephen Stoneburn
President, Digital & CFO Douglas E. Grose
President, CEO Alan J. Imhoff
President, Custom Solutions JoAnn Wahl
Senior Vice President, Finance Steven J. Resnick
Vice President, Operations Jim Chicca
Vice President, Audience Development Donna Sickles
Vice President, Custom Programs Carol Nathan
Vice President, Custom Solutions Wendy Raupers
Vice President, eBusiness Development Lee Schweizer
Vice President, Human Resources & Facility Operations Carolyn Caccavelli
Vice President, Marketing & Customer Advocacy Jim McDonough
Vice President, Sales Mike Guire
Vice President, Society Partners Mark Branca
Corporate Director, Research & Communications Lori Raskin
In affiliation with Global Academy for Medical Education, LLC
Vice President, Medical Education & Conferences Sylvia H. Reitman, MBA
Vice President, Events David J. Small, MBA



Scan this QR Code to visit chestnet.org/chestphysician

Continued from previous page

the other half of patients.

One possible reason is that some manifestations of the disorder are not driven by eosinophils. Another is that nonresponsive patients may have sustained longstanding, irreversible vasculitic damage that is no longer amenable to anti-interleukin-5 therapy.

Alternatively, it's possible that mepolizumab reduced eosinophils in the blood but not those in the body tissues of nonresponsive patients or that the patients who didn't respond well simply required a higher dose of the drug, Dr. Wechsler and his associates said.

The NIAID is now supporting a study of blood, urine, sputum, and tissue samples from some of these participants "to address questions related to disease risk and pathological features, as well as response to treatment," they added.

Many authors reported receiving payments from pharmaceutical companies, including several from GlaxoSmithKline. Four authors are employees of the company.

VIEW ON THE NEWS

Directions for future research

The study by Michael E. Wechsler, MD, and his associates can be considered proof of concept. Now, researchers must turn to identifying biomarkers that predict the success or failure of mepolizumab in patients.

Researchers must also elucidate the fate of eosinophils in the tissues, especially in vasculitic lesions, after treatment with mepolizumab. And they should address possible synergistic activity when the drug is given together with immunosuppressants such as azathioprine and cyclophosphamide.

In addition, future studies should include patients who have organ-threatening or life-threatening eosinophilic granulomatosis with polyangiitis, who were excluded from

this trial but who are most in need of novel treatments.

Ratko Djukanovic, MD, is with the University of Southampton (England) and the National Institute for Health Research Southampton Biomedical Research Centre. Paul M. O'Byrne, MD, is with the Firestone Institute for Respiratory Health within St. Joseph's Healthcare and McMaster University in Hamilton, Ont. Dr. Djukanovic and Dr. O'Byrne both reported financial relationships with pharmaceutical companies outside their editorial. They made these remarks in an editorial accompanying Dr. Wechsler and colleagues' report (N Engl J Med. 2017 May 18. doi: 10.1056/NEJM1704402).

Serum tryptase down by 43%

Imatinib from page 1

and it is elevated in the bronchoalveolar lavage fluid from patients with uncontrolled asthma.

To examine whether imatinib would decrease mast-cell counts and activation in the airways of adults with severe, refractory asthma, the investigators performed the randomized double-blind proof-of-principle trial at seven academic centers across the United States over the course of 5 years.

A total of 62 patients were assigned to 24 weeks of either oral imatinib (32 participants) or a matching placebo (30 participants). Fifty patients, 24 in the imatinib group and 26 in the placebo group, completed the trial.

The primary outcome measure

was the change in airway hyperresponsiveness at 6 months, as measured by the increase in the concentration of methacholine that causes significant bronchoconstriction (PC_{20}).

Imatinib decreased airway hyperresponsiveness to a greater degree than did placebo. Imatinib increased PC_{20} by a mean of 1.20 doubling doses at 3 months and by a mean of 1.73 doubling doses at 6 months, compared with 0.03 and 1.07, respectively, for placebo.

The small improvement in the placebo group is consistent with a phenomenon reported in other studies, in which patients show a delayed improvement in airway hyperresponsiveness for several months after they started inhaled glucocorticoids, Dr. Cahill and her associates noted (N Engl J Med. 2017 May 18. doi: 10.1056/NEJMoa1613125).

Imatinib also reduced mast-cell activity as measured by serum and airway levels of tryptase. Serum tryptase decreased by 43% in the imatinib group, compared with a 12% decline in the placebo group. And tryptase levels in bronchoalveolar lavage fluid tended to decrease in the imatinib group but to increase in the placebo group.

Imatinib also increased mean forced expiratory volume in 1 second (FEV_1).

"Although the increase in FEV_1 may not seem substantial, it suggests that mast-cell-dependent processes contribute to airway obstruction in these patients despite high-dose, anti-inflammatory gluco-

corticoid therapy. The near-50-mL difference in the change in baseline FEV_1 between the imatinib and placebo groups is small, but it is likely to be important in light of the population we studied," Dr. Cahill and her associates wrote.

In addition, exploratory analyses showed that the reduction in airway

The near-50-mL difference in the change in baseline FEV_1 between the imatinib and placebo groups is small, but it is likely to be important in light of the population we studied, the authors wrote.

hyperresponsiveness with imatinib "negatively correlated with baseline blood eosinophil counts, and baseline numbers of neutrophils in bronchoalveolar lavage fluid were strongly correlated with increases in FEV_1 . Together, these findings support a role for mast cells in non-eosinophilic asthma. Since almost half of the patients with severe asthma have neutrophilic airway inflammation, we speculate that KIT inhibition might represent an important approach to treatment for this group," they said.

This study was supported by the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, the Vinik family, and the Kaye family; Novartis provided imatinib free of charge.

The authors' financial disclosures are available at www.nejm.org.

VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: This study

presents important findings that continue to deepen our understanding of the key factors in the different phenotypes of asthma.

The authors point out that this sets the stage for further research in the exploration of targeted therapies that could help some of our sickest and most difficult-to-treat asthmatic patients.



CHEST
Annual Meeting
2017



TORONTO
CANADA

October 28 - November 1

CHEST Annual Meeting is your connection to education opportunities that will help optimize your patient care. Hundreds of clinically relevant sessions and the community of innovative problem-solvers who attend will inspire and energize you and your career.

Learn More
chestmeeting.chestnet.org

Invasive mediastinal staging for high-risk NSCLC

BY MARK S. LESNEY
Frontline Medical News

Endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA) appears to be cost effective for use in non-small cell lung cancer (NSCLC) staging if the prevalence of mediastinal lymph node metastasis (MLNM) is greater than or equal to 2.5%, according to the results of single institution modeling study. In addition, the study found that confirmatory mediastinoscopy should be performed in high-risk patients in cases of negative EBUS-TBNA.

Katarzyna Czarnecka-Kujawa, MD, of the University of Toronto and Toronto General Hospital, and

her colleagues performed a decision analysis to compare health outcomes and costs of four mediastinal staging strategies. They assessed the following: no invasive staging, endobronchial ultrasound-guided

transbronchial need aspiration, mediastinoscopy, and EBUS-TBNA followed by mediastinoscopy if EBUS-TBNA results were negative. They determined incremental cost-effectiveness ratios (ICER) for

all strategies and performed comprehensive sensitivity analyses using a willingness to pay threshold of \$80,000 (Canadian)/quality-adjusted life-year (QALY).

They used data obtained for

Flu shots may spark adverse events in NSCLC

BY NEIL OSTERWEIL
Frontline Medical News

GENEVA – The influenza vaccine may interact with immune checkpoint inhibitors in patients with lung cancer, results of a small study suggest.

Among 23 patients with non-small cell lung cancer (NSCLC) treated with a drug targeted against programmed death-1 (PD-1), the seasonal flu vaccine appeared to produce good serologic protection against infection, but at the possible cost of an increase in the rate of immune-related adverse events (IrAE), reported Sacha Rothschild, MD, PhD, of University Hospital Basel (Switzerland) at the European Lung Cancer Conference.

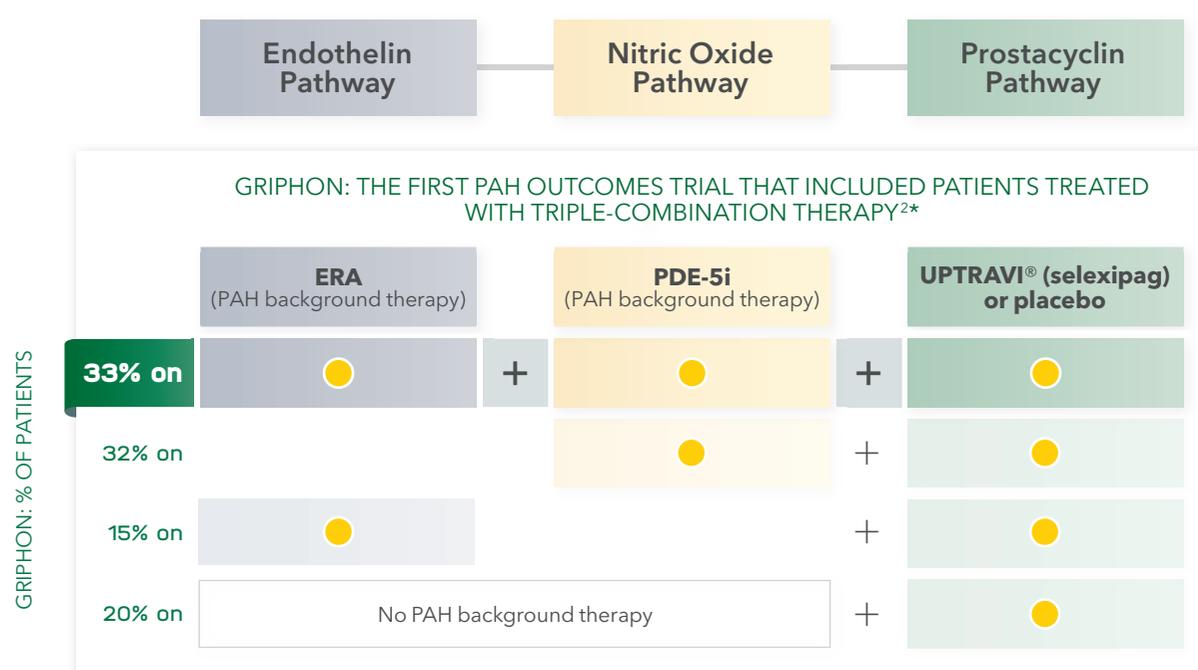
“Over 50% of patients overall had an immune-related adverse event, and that’s certainly higher than what we have seen in all the studies, and it’s also clearly higher than what we see in our daily clinical practice, especially with grade 3/4 toxicity,” he said in an interview at the meeting.

Among 23 patients with lung cancer treated with a PD-1 inhibitor, 12 (52.2%) had one or more IrAEs. In contrast, the most frequent IrAE in a key registration trial for nivolumab (Opdivo) was skin rash, which occurred in 9% of patients (N Engl J Med. 2015 Jul 9;373:1627-39).

“It’s a very small study, but it raises some concern that there might be an interaction between the vaccine and PD-1 blockade,” Dr. Rothschild said.

IN PAH (WHO GROUP I), 3 Key Pathways Are Targeted for Treatment¹

Triple UP
3 Oral Therapies for 3 Pathways



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

• 2015 ESC/ERS Guidelines recommend UPTRAVI added to ERA and/or PDE-5i for efficacy of sequential combination therapy in FC II and FC III PAH (WHO Group I)³

INDICATION

UPTRAVI 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.

ADVERSE REACTIONS

Adverse reactions occurring more frequently ($\geq 3\%$) 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.

Please see additional Important Safety Information on adjacent page.

*UPTRAVI in combination with an ERA and PDE-5i.

staging, outcomes, and costs from the patients in the lung cancer program at the Toronto General Hospital from Jan. 1, 2005, to Dec. 31, 2014, as detailed in a report published in the June issue of the *Journal of Thoracic and Cardiovascular Surgery* (2017. doi: 10.1016/j.jtcvs.2016.12.048).

After exclusions, they utilized a final case count of 499 cases for developing their surgical and procedure cost analysis, and a total of 750 cases in their endoscopy database for endoscopy analysis. For the base-case analysis, they assumed a prevalence of mediastinal metastasis of 9%, and obtained the prevalence of a pathologic lymph nod-

al stage disease following EBUS-TBNA from their institutional data.

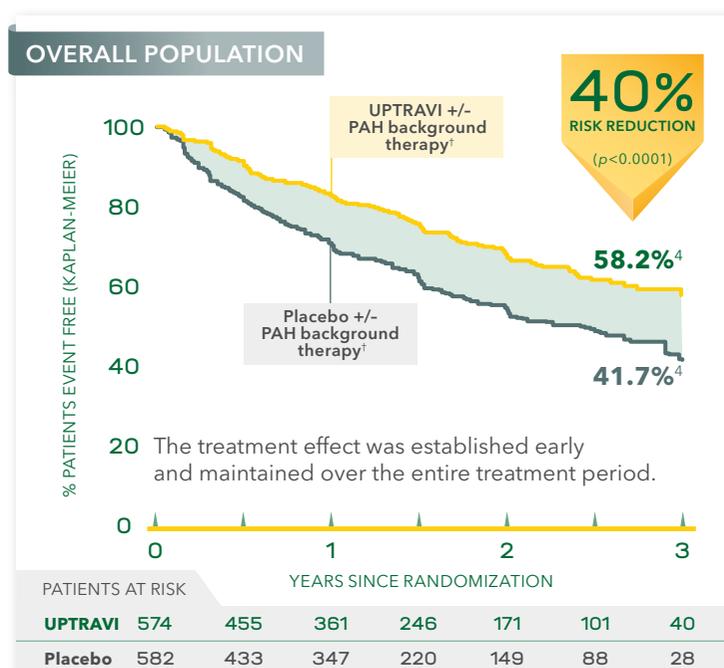
Their results showed that EBUS-TBNA followed by mediastinoscopy was the strategy that resulted in the highest QALYs, but that it had a prohibitive ICER of greater than \$1.4 million/QALY. Accordingly, it may not be justifiable to use medi-

astinoscopy after negative EBUS-TBNA in all patients, the researchers noted. However, the researchers' data suggest that invasive screening may be justified in a very-low-risk population (MLNM above 2.5%).

In addition, the researchers stated that "[the] benefit conveyed
Continued on following page

Consistent Treatment Effect on Time to First Disease Progression Event, Irrespective of PAH Background Therapy²

PRIMARY ENDPOINT: TIME TO FIRST DISEASE PROGRESSION EVENT IN GRIPHON



A primary endpoint event was experienced by 27.0% (155/574) of UPTRAVI-treated patients vs 41.6% (242/582) of placebo-treated patients.

Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo):

- Hospitalization for PAH (13.6% vs 18.7%)
- Other disease progression events (6.6% vs 17.2%)[†]
- Death (4.9% vs 3.1%)
- Initiation of parenteral prostanoid or chronic oxygen therapy (1.7% vs 2.2%)
- PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%)

Reductions in PAH-related hospitalization and other disease progression events[‡] drove an overall 40% risk reduction.

Add UPTRAVI to an ERA + PDE-5i for All-oral TRIPLE-combination Therapy

IMPORTANT SAFETY INFORMATION (cont'd)

DOSAGE AND ADMINISTRATION

Recommended Dosage

Recommended starting dose is 200 mcg twice daily. Tolerability may be improved when taken with food. Increase by 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily. If dose is not tolerated, reduce to the previous tolerated dose.

Patients with Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 mcg once daily. Increase by 200 mcg once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).

Dosage Strengths

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

Please see Brief Summary of Prescribing Information on the following page.

[†]An ERA, PDE-5i, or both.

[‡]Other disease progression defined as a 15% decrease from baseline in 6MWD plus worsening of Functional Class or need for additional PAH-specific therapy.

6MWD=6-minute walk distance; ERA=endothelin receptor antagonist; ERS=European Respiratory Society; ESC=European Society of Cardiology; PDE-5i=phosphodiesterase type-5 inhibitor; WHO=World Health Organization.

References: 1. Humbert M, Lau EM, Montani D, et al. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation*. 2014;130(24):2189-2208. 2. UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc. December 2015. 3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46(4):903-975. 4. Data on file, Actelion Pharmaceuticals.

Visit www.UPTRAVI.com/hcp to learn more

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



UPTRAVI is a registered trademark of Actelion Pharmaceuticals Ltd
©2017 Actelion Pharmaceuticals US, Inc. All rights reserved. SLX-00337 0217

Continued from previous page

by detecting mediastinal metastatic disease becomes more apparent as the prevalence of MLNM increases, with confirmatory mediastinoscopy becoming cost effective in cases of negative EBUS-TBNA in patients with moderate to high probability of

MLNM" (greater than 57%).

Our model points out that there is a well-defined role for the use of different modalities, including mediastinoscopy. This stresses the need for ongoing focus on maintenance of competency and skill acquisition in mediastinoscopy and EBUS-TBNA by currently practicing and future

thoracic surgeons respectively," the researchers concluded.

Dr. Czarnecka-Kujawa disclosed that she is a research consultant with Olympus America. The study was funded in part by agencies of the Austrian government.

mlesney@frontlinemedcom.com



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%).

DOSE 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 $\geq 3\%$: headache 65% vs 32%, diarrhea 42% vs 18%, jaw pain 26% vs 6%, nausea 33% vs 18%, myalgia 16% vs 6%, vomiting 18% vs 9%, pain in extremity 17% vs 8%, flushing 12% vs 5%, arthralgia 11% vs 8%, anemia 8% vs 5%, decreased appetite 6% vs 3%, and rash 11% vs 8%.

These adverse reactions are more frequent during the dose titration phase.

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.

Laboratory Test Abnormalities

Hemoglobin

In a Phase 3 placebo-controlled study in patients with PAH, mean absolute changes in hemoglobin at regular visits compared to baseline ranged from -0.34 to -0.02 g/dL in the selexipag group compared to -0.05 to 0.25 g/dL in the placebo group. A decrease in hemoglobin concentration to below 10 g/dL was reported in 8.6% of patients treated with selexipag and 5.0% of placebo-treated patients.

Thyroid function tests

In a Phase 3 placebo-controlled study in patients with PAH, a reduction (up to -0.3 MU/L from a baseline median of 2.5 MU/L) in median thyroid-stimulating hormone (TSH) was observed at most visits in the selexipag group. In the placebo group, little change in median values was apparent. There were no mean changes in triiodothyronine or thyroxine in either group.

DRUG INTERACTIONS

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

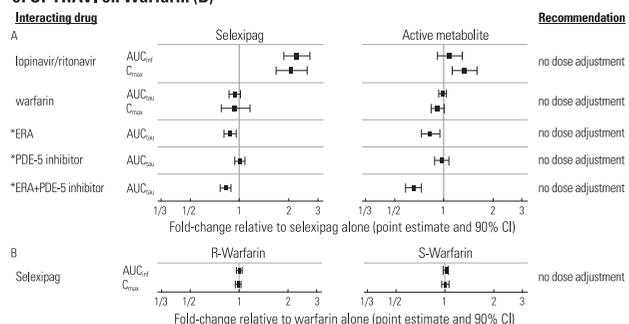
Selexipag is hydrolyzed to its active metabolite by hepatic carboxylesterase 1. Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates 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.
UPTRAVI is a registered trademark of Actelion Pharmaceuticals Ltd
© 2016 Actelion Pharmaceuticals US, Inc. All rights reserved.
SLX-00099 0416



VIEW ON THE NEWS

Endobronchial US appears to remain the method for all seasons

The authors make a compelling argument for invasive mediastinal staging in patients with clinical stage I non-small cell lung cancer and acknowledge that this conflicts with current guidelines, according to Biniam Kidane, MD, of the University of Manitoba, Winnipeg, in his invited comments on the study in the Journal of Thoracic and Cardiovascular Surgery (2017 Mar 10. doi: 10.1016/j.jtcvs.2017.02.051).



Their single-payer system is likely to have a different willingness-to-pay threshold, compared with those in other countries, especially the United States, where the EBUS-TBNA strategy without invasive staging is likely to remain the cost-effective choice.

Dr. Kidane applauded the authors on their methodologically rigorous analysis with robust sensitivity analyses to capture a wide range of mediastinal lymph node metastasis (MLNM) prevalence and EBUS-TBNA proficiencies and "provide a brilliant pictorial representation of their analyses that allows readers to identify the most cost-effective strategy by finding the intersection of their local MLNM prevalence and EBUS sensitivities.

"Cost-economic analyses such as these provide a window into the factors necessary to bridge guidelines from the realm of the abstract to the realm of local reality. When interpreting these findings, clinicians should consider: (1) What EBUS resources are available? (2) What is your local EBUS sensitivity? (3) What is the prevalence of MLNM?" Dr. Kidane concluded, with the caveat that such studies are not infallible and models are based on assumptions and must be treated with care.

Dr. Kidane reported no disclosures with regard to commercial support.

SYNDROMIC TESTING FROM BIOFIRE:

Improve Patient Outcomes.

BioFire's syndromic testing allows you to quickly identify infectious agents that produce similar symptoms in patients. BioFire's innovative PCR technology provides answers in a clinically actionable timeframe using any of the FilmArray® Panels:

-  **Respiratory Panel:** Enable a faster, more informed diagnosis that can reduce the usage and duration of antibiotic administration and decrease length of hospital stay.
-  **Blood Culture Identification Panel:** Reduce time to effective therapy and antimicrobial de-escalation which may improve patient survival rates.
-  **Gastrointestinal Panel:** Quickly ruling in or out enteric pathogens may improve patient care by preventing misdiagnosis and mistreatment.
-  **Meningitis/Encephalitis Panel:** Quickly identifying a CNS infection as viral, bacterial or fungal may reduce patient mortality.

To learn how syndromic testing from BioFire can help YOU improve patient outcomes, visit biofiredx.com

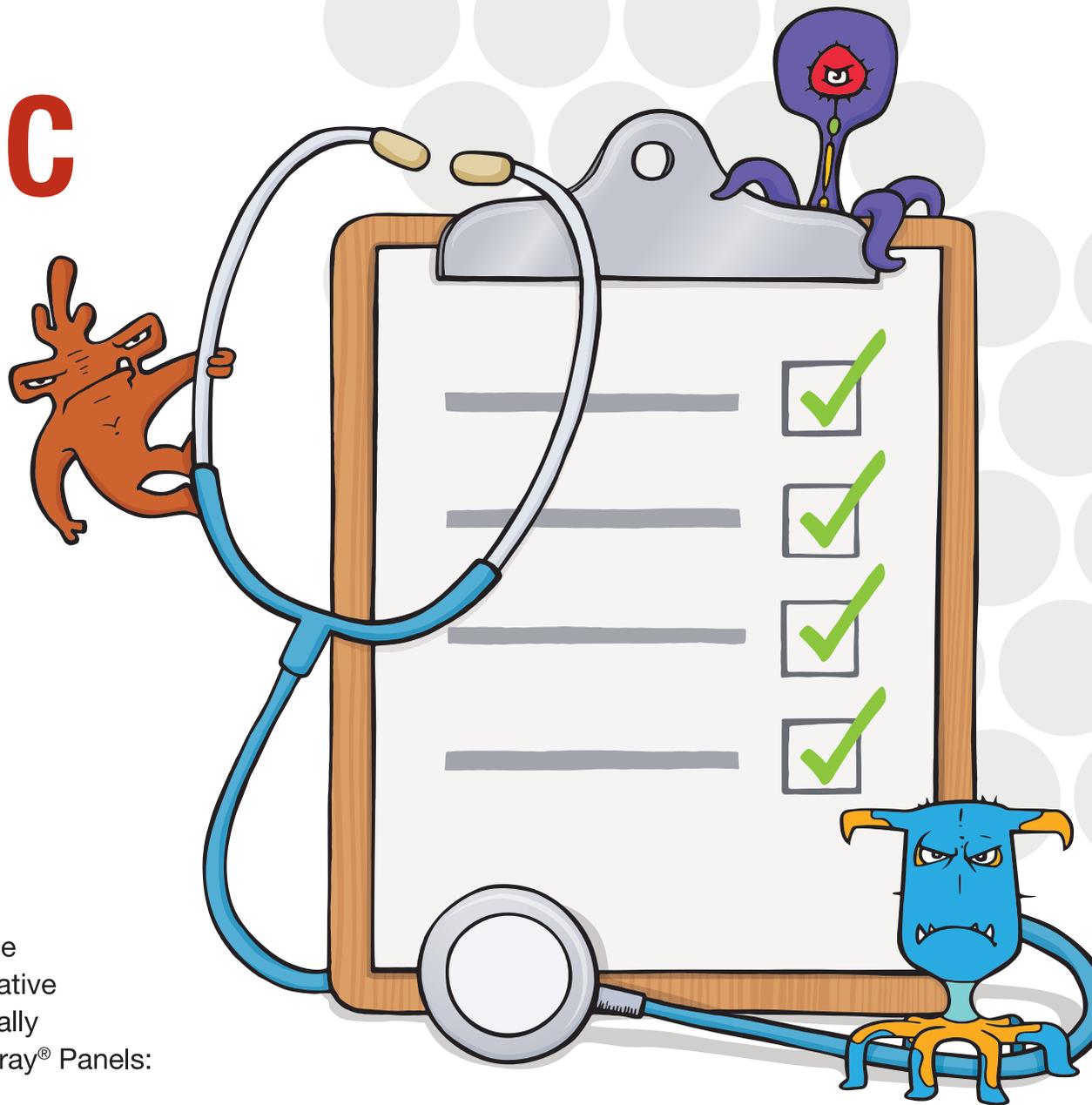
Data on file at BioFire Diagnostics.



A BIOMÉRIEUX COMPANY

Syndromic Testing: The Right Test, The First Time.

Respiratory • Blood Culture Identification • Gastrointestinal • Meningitis/Encephalitis



Sleep disorder diagnoses less common in women

BY ELI ZIMMERMAN
Frontline Medical News

Women are less likely to be diagnosed with and treated for sleep-disordered breathing, despite having symptoms similar to those of men, a Swedish study showed.

In a survey of 10,854 subjects, 14% of women reported being diagnosed with obstructive sleep apnea (OSA), compared with 25% of men (P less than .001), and 9% of women reported having any OSA treatment, compared with 16% of men (Sleep Med. 2017. doi: 10.1016/j.sleep.2017.02.032).

Underdiagnosis of sleep-disordered breathing (SDB) in women may have dire consequences, as symptoms, specifically snoring and excessive daytime sleepiness (EDS), correlate with increased risk for hypertension and diabetes, regardless of gender, according to Eva Lindberg, PhD, professor in the department of medical sciences, respiratory, allergy, and sleep research at Uppsala (Sweden) University, and her colleagues.

The mean age of the patients at baseline was 41 years. Mean body mass index was 25.4 kg/m² for men and 24 kg/m² for women.

On initial testing, approximately three times the percentage of men reported having issues with snoring and no EDS, compared with women (19% vs. 6% respectively), while more women reported the opposite, EDS but no snoring (19% vs. 11%). A slightly larger percentage of men reported having both symptoms (7.3% vs. 4.5%).

Investigators hypothesized the disparity be-

tween women and men reporting problems with snoring may be caused by gender expectations.

"It is more probable that SDB is still assumed to be a condition associated predominantly with men, and women feel ashamed of reporting these symptoms and seeking medical advice," said Dr. Lindberg and her coinvestigators. These gender expectations may "contribute to females being less inclined to seek medical advice due to SDB symptoms."

In a follow-up survey conducted 11 years after the initial one, doctors found 1,716 and 319 patients had received a new diagnosis for hypertension and diabetes, respectively.

While incidence was greater in men than in women for both (hypertension: 18.6% vs. 15.8% [P less than .001] and 3.6 vs. 2.4% [P less than .001], respectively), the investigators found "after adjusting for BMI and snoring at baseline, none of these gender differences remained significant."

Physicians' perception of SDB is partially responsible for the number of women who go undiagnosed, according to the researchers. Because SDB is considered to occur predominantly in males, doctors may overlook symptoms in female patients that would otherwise be a cause for further testing, they noted.

"[Even] among health professionals, SDB is still usually attributed to a male population, and female patients are therefore less frequently asked about the cardinal symptoms of snoring and sleepiness and do not therefore undergo sleep recordings. ... Also, among patients with obesity hypoventilation syndrome, females are

generally diagnosed when the disease is more advanced and significantly more frequently develop acute disease before achieving treatment," the investigators wrote.

Dr. Lindberg and her team suggested engaging female patients more frequently about SDB symptoms, as well as referring patients with positive symptoms to participate in a sleep study.

The current study was limited by the nature of the data, which were self-reported. Patients were not surveyed via the Epworth Sleepiness Scale.

The study was funded by grants from the Norwegian Research Council, the Icelandic Research Council, Aarhus University, the Swedish Heart-Lung Foundation, and the Estonian Science Foundation.

The investigators reported no relevant financial disclosures.

ezimmerman@frontlinemedcom.com
On Twitter @eaztweets

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: The authors discuss the important topic of differing expression of OSA in male versus female subjects that may lead to under-recognition of sleep apnea in women.



Oxygen desaturation index produces disparate data

BY ELI ZIMMERMAN
Frontline Medical News

WASHINGTON – Oxygen desaturation index (ODI) scores showed significant variation across two software systems, a study showed.

The researchers assessed the ODI scores of 106 patients using the ResMed ApneaLink Plus system (AL) and the Compumedics Grael Profusion PSG3 system (Comp). "AL ODI values tended to be higher than Comp ODI values, but with significant variability," they said.

AL showed a bias of an additional 4.4 events per hour (95% limits of agreement, -5.8 to 14.6 events per

hour) for ODI scores at 4% desaturation and a bias of an additional 7.1 events per hour (95% limits of agreement, -6.4 to 20.6 events per hour) at 3% desaturation (J Clin Sleep Med. 2017;13[4]:599-605).

This may be problematic for physicians evaluating patients during sleep studies who rely on ODI scores at 3% and 4% desaturations to create accurate apnea severity assessments, the investigators said.

"[The] wide limits of agreement in our study highlight that clinicians cannot be confident that an ODI4% recorded in the AL is the same as that recorded in the Comp," wrote Yvonne Ng, MBBS, of the department of lung and sleep medicine at Monash Health, Victoria, Australia, and her colleagues. "The differences are large enough to significantly affect diagnostic thresholds for OSA [obstructive sleep apnea] and, in particular, moderate-severe OSA."

The researchers gathered data from patients undergoing sleep analysis at the Monash Medical Centre, who

were, on average, 47 years of age, had a body mass index score of 32 kg/m², and had an apnea hypopnea index (AHI) of 23.2.

ODI3% scores analyzed through Comp diagnosed 66 patients with OSA (ODI3% greater than or equal to 5 events per hour), while desaturation events analyzed through the AL system diagnosed 90 patients, a 36% increase over Comp (P = .0002).

When researchers tested for moderate to severe OSA (ODI3% greater than or equal to 15 events per hour), 32 patients were diagnosed using the Comp system, compared with 59 patients using the AL system.

Disparities in these measurements create uncertainty among clinicians, who rely on ODI measurements for scores that are accurate and can be easily replicated using an algorithm, the researchers said.

"The current work demonstrates that significantly more patients would receive a diagnosis of OSA, or more particularly, moderate-severe OSA, with the AL ODI, compared to

the Comp ODI," Dr. Ng and her colleagues wrote.

When sensitivity scores for Comp and AL were compared, AL ODI3% scores were significantly more sensitive than Comp, with sensitivity scores of 96% vs. 58%.

Using different fingers for measuring desaturation during the test or differences in algorithms used to assess ODI scores were possible sources of the disparities, the researchers noted. Differences in internal processing between the two systems were the most likely causes of the discrepancies between the data collected using each system, they added.

Because there is no universal standard for ODI measurements, the researchers were unable to determine which system was more accurate.

Several of the researchers reported receiving financial support, research equipment, or consultancy fees from various entities.

ezimmerman@frontlinemedcom.com
On Twitter @eaztweets

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: This article raises significant concerns about the role of different oximeters in contributing to the variation in hypopnea scoring.

Patients accepted side effects

Chronic cough from page 1

complete loss of taste.

However, only 6 patients out of 63 who were randomized to this dosage stopped taking their medication.

The finding suggests that the drug was tolerable for most of the patients.

The results also suggested that lower dosages with less potent adverse effects on taste produced significant cough reductions in some patients.

“Patients with chronic, refractory cough are often “willing to accept some taste change to reduce their cough count.



MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Jaelyn A. Smith

“Patients are willing to put up with the taste side effects,” Dr. Smith said in a video interview.

The study enrolled patients with chronic, refractory cough at U.S. and U.K. centers and randomized 63 to each of three active treatment arms receiving 7.5 mg, 20 mg, or 50 mg b.i.d. of MK-7264 or to placebo for 12 weeks.

The patients averaged 60 years of age and about three-quarters were women.

On average, they had their cough for more than 10 years, and these patients coughed roughly 30 times an hour when awake.

The study’s primary endpoint was reduction in awake cough frequency, and, after 12 weeks on treatment with 50 mg b.i.d., this had fallen an average of 37%, compared with placebo, said Dr. Smith, who is a professor of respiratory medicine at the University of Manchester (England).

The 7.5-mg and 20-mg b.i.d. dosages each led to cough frequency reductions of about 22% over placebo

that were not statistically significant. This was likely a result of the unexpectedly strong placebo effect in the study, Dr. Smith said.

Most of the cough effect was

evident after the first 4 weeks on treatment.

Dr. Smith noted that she and her associates “most definitely” plan to progress to a phase III trial. “We really lack effective treatments for cough,” she said.

The study was sponsored by Merck, the company that is

developing MK-7264.

Dr. Smith is a consultant with Merck and has a licensing agreement with Vitalograph. A video interview with her on this topic is available at mdedge.com/chestphysician.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

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

⁴Based on IMS data of prescriptions for new patients from March 2015 through February 2016.
See SUN Study design on next page.

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

Stage IV sarcoidosis differs in blacks and whites

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – Black patients with advanced-stage sarcoidosis generally have a pattern of fibrotic scar

in their lungs that is different from that of whites, a finding with potentially important implications for prognosis and management.

Systematic assessment of 349 American patients diagnosed with

sarcoidosis – 264 whites and 85 blacks – showed that black patients had nearly double the prevalence of advanced, end-stage, Scadding stage IV fibrosis in their lungs, with a 19% rate among whites and a 34% rate

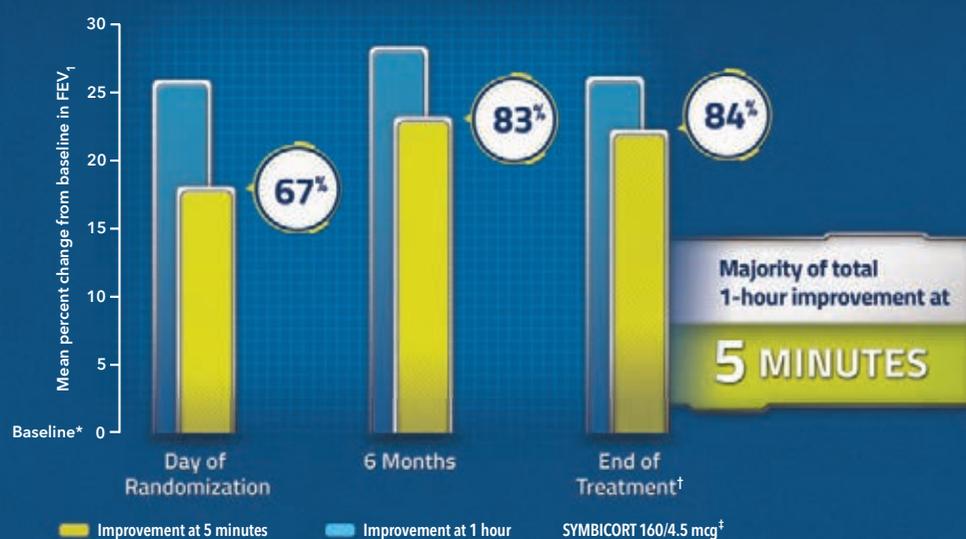
among blacks, confirming that blacks generally have worse sarcoidosis, Andy Levy, MD, said at an international conference of the American Thoracic Society.

All these sarcoidosis patients par-

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



This research confirmed that black patients generally have worse sarcoidosis than white patients.

DR. LEVY

participated in the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study, and underwent CT scanning as part of the study's protocol. The scans showed that 16 of the 29 black patients with stage IV disease (19% of the total group of 85) had a "honeycomb" structure to their fibrotic scar, com-

pared with 10 of the 50 white patients (4% of the total group of 264).

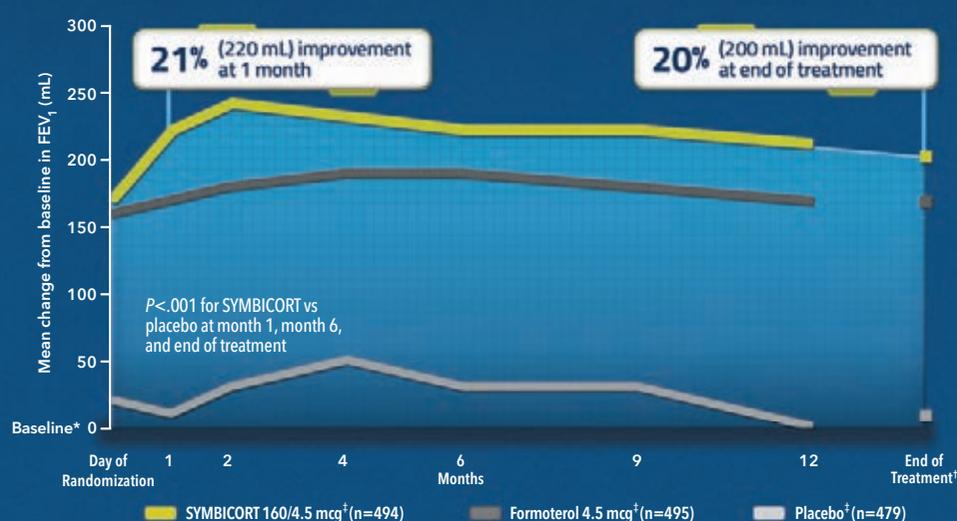
Honeycomb scar is associated with more restrictive disease, characterized by reduced total lung capacity and reduced diffusing capacity of the lungs for carbon monoxide, features seen in these black stage IV patients, said Dr. Levy, a pulmonologist at

National Jewish Health in Denver. Bronchovascular distortion, the more common scar pattern seen in the white patients, results in more obstructive symptoms, such as a reduced ratio of forced expiratory volume in 1 second to forced vital capacity, which Dr. Levy reported as

Continued on following page

Sustained effect. Control over 12 months.^{1,2}

Improvement in 1-hour postdose FEV₁ over the 12-month study²



» SYMBICORT 160/4.5 significantly improved pre-dose 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%).

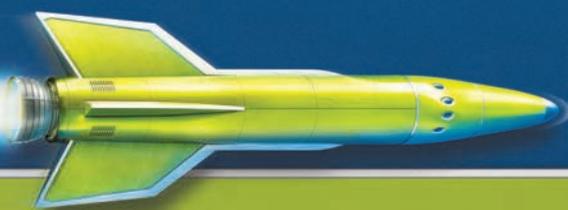
SYMBICORT 160/4.5 mcg[†] (n=494), formoterol 4.5 mcg[†] (n=495), placebo[†] (n=479).

*Baseline is defined as the pre-dose 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

SYMBICORT is a registered trademark of the AstraZeneca group of companies.
©2016 AstraZeneca. All rights reserved. 3269108 7/16

Continued from previous page

a characteristic of the white GRADS patients.

Even though the pulmonary fibrosis was end stage in all the black and white stage IV patients examined, “where the scar occurs may depend on genetics or environment, and may

affect how the disease manifests. We don’t fully know what it means yet,” Dr. Levy said in an interview. “There is this difference in the sarcoidosis of some black patients compared with white patients that needs further investigation to figure out why the scar is different.”

The different distribution of

Even though the pulmonary fibrosis was end stage in all the black and white stage IV patients examined, “where the scar occurs may depend on genetics or environment, and may affect how the disease manifests,” Dr. Levy noted.

lung fibrosis in blacks and whites “could have huge implications for prognosis and management,” said

Laura Koth, MD, a pulmonologist and professor at the University of California, San Francisco, and lead

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use
BRIEF SUMMARY of PRESCRIBING INFORMATION
For full Prescribing Information, see package insert.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [see Warnings and Precautions (5.1)].

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see Warnings and Precautions (5.1) in the full Prescribing Information]. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only strength indicated for the treatment of airflow obstruction in COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Asthma-Related Death

LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABA, including formoterol, one of the active ingredients in SYMBICORT. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Deterioration of Disease and Acute Episodes

SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. SYMBICORT has not been studied in patients with acutely deteriorating asthma or COPD. The initiation of SYMBICORT in this setting is not appropriate.

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment

regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive Use of SYMBICORT and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled drugs containing beta₂-adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Pneumonia and Other Lower Respiratory Tract Infections

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids.

In a 6-month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1%) compared with placebo (1.3%). In a 12-month study of 1,964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIg), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (see the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta₂-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing

investigator for the study reported by Dr. Levy.

The GRADS data collection also showed that a significantly higher percentage of black patients had most recently received prednisone treatment for their sarcoidosis, 45% compared with 29% in whites, Dr. Levy reported. Ideally most

sarcoidosis patients would be on a steroid-sparing regimen, such as methotrexate. The excess prednisone treatment the black patients received confirmed prior reports of treatment disparities by race among American sarcoidosis patients, he said.

GRADS includes patients enrolled at seven U.S. research centers. The

study's primary goal is to try to identify "genomic signatures" that link with the clinical phenotypes identified through spirometry, bronchoscopy, CT scans, and physical examinations, Dr. Koth explained. The investigators plan to enroll more patients into the program to validate the findings, she said. "This is an

early stage, but we have seen some signals we want to follow-up."

GRADS is funded by the National Heart, Lung, and Blood Institute. Dr. Levy and Dr. Koth had no relevant financial disclosures.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol

2

the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information].

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see Overdosage (10) in the full Prescribing Information]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, 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 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information].

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see Clinical Pharmacology (12.2) in the full Prescribing Information]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see Warnings and Precautions (5.1) in the full Prescribing Information].

Systemic and inhaled corticosteroid use may result in the following:

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

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

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV₁ at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

CRT-D helpful in mild HF with high ejection fraction

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – Patients with mild heart failure symptoms, left bundle branch block, and a left ven-

tricular ejection fraction of 31%-44% who received cardiac resynchronization therapy with a built-in defibrillator experienced a significant reduction in all-cause mortality, compared with those randomized to an

implantable cardioverter-defibrillator alone during 7 years of follow-up.

These results from a new MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

long-term follow-up substudy “suggest that patients with a relatively preserved ejection fraction greater than 30% benefit from a CRT-D [cardiac resynchronization therapy defibrillator] and could potentially be considered for this therapy,” said Katherine Vermilye, MD, at the annual meeting of the American College of Cardiology.

This represents a broadening beyond the conclusions earlier reached in the landmark MADIT-CRT. In the primary report, MADIT-CRT investigators concluded that CRT-D significantly reduced the risk of heart failure events, compared with an implantable cardioverter defibrillator (ICD) alone during an average follow-up of 2.4 years in patients with mild symptoms of either ischemic or nonischemic cardiomyopathy, a wide QRS duration, an left ventricular ejection fraction (LVEF) of 30% or less, and left bundle branch block, but not in those who didn't have left bundle branch block (N Engl J Med. 2009 Oct 1;361[14]:1329-38).

In a subsequent publication, the MADIT-CRT investigators reported that, with extension of follow-up to 7 years, CRT-D also provided a significant benefit in terms of all-cause mortality in addition to the reduced rate of heart failure events (N Engl J Med. 2014 May 1;370[18]:1694-701).

However, even though an LVEF of 30% or less was a requirement for participation in MADIT-CRT, it turned out that, when the initial screening echocardiograms were eventually analyzed in a central core laboratory, one-third of study participants actually had a baseline LVEF of 31% to 44%, with the majority of excessive values being in the 31%-35% range.

Dr. Vermilye, of the University of Rochester in New York, presented a post hoc analysis of long-term outcomes in the subgroup having a baseline LVEF greater than 30%. They totaled 450 of 1,224 MADIT-CRT participants with left bundle branch block. They were significantly older

Continued on following page

SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol

3

Table 1 Adverse reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment [†]	SYMBICORT		Budesonide		Formoterol		Placebo
	80/4.5 N = 277	160/4.5 N = 124	80 mcg N = 121	160 mcg N = 109	4.5 mcg N = 237	N = 400	
Adverse Event	%	%	%	%	%	%	%
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9	

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of $\geq 3\%$ and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV₁ at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of $\geq 3\%$ in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of $\geq 3\%$ and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment [†]	SYMBICORT		Budesonide		Formoterol		Placebo
	160/4.5 N = 771	160 mcg N = 275	4.5 mcg N = 779	N = 781	N = 781	N = 781	
Adverse Event	%	%	%	%	%	%	
Nasopharyngitis	7.3	3.3	5.8	4.9	4.9	4.9	
Oral candidiasis	6.0	4.4	1.2	1.8	1.8	1.8	
Bronchitis	5.4	4.7	4.5	3.5	3.5	3.5	
Sinusitis	3.5	1.5	3.1	1.8	1.8	1.8	
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7	2.7	2.7	
Average Duration of Exposure (days)	255.2	157.1	240.3	223.7			

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness

Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta₂-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) [see *Warnings and Precautions* (5.9) in the full Prescribing Information].

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage of the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see *Warnings and Precautions* (5) in the full Prescribing Information]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

SYMBICORT is a trademark of the AstraZeneca group of companies.

©AstraZeneca 2017

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: AstraZeneca Dunquerque Production, Dunquerque, France

Product of France

Rev. 01/2017 3327037 2/17

VIEW ON THE NEWS

Frank Podbielski, MD, FCCP, comments: The authors demonstrate the benefit of cardiac resynchronization therapy in patients with a defibrillator. The reduction in mortality at 5 years was greater in high responders to CRT-D, although overall mortality was significantly reduced in all comers.

A transdermal mitral valve replacement pipe dream

BY BRUCE JANCIN
Frontline Medical News

SNOWMASS, COLO. – Percutaneous mitral valve replacement is unlikely to ever catch on in any way remotely approaching that of transcatheter aortic valve replacement for the treatment of aortic stenosis, Blase A. Carabello, MD, predicted at the Annual Cardiovascular Conference at Snowmass.

“We’ve spent \$2 billion looking for methods of percutaneous mitral valve replacement, and yet, I have to wonder if that makes any sense,” said Dr. Carabello, professor of medicine and chief of cardiology at East Carolina University in Greenville, N.C.

“If repair is superior to replacement in primary MR [mitral regurgitation], which I think we all agree is true, and you don’t need to get rid of every last molecule of blood going backward across the mitral valve when you’ve got a good left ventricle, then a percutaneous replacement in primary MR would have only the niche of patients who are inoperable and whose leaflets can’t be grabbed by the MitraClip or some new percutaneous device down the road. And, in secondary MR, it doesn’t seem to matter whether you replace or repair the valve, so why not just repair it with a clip?” he argued.

Numerous nonrandomized studies have invariably demonstrated superior survival for surgical repair versus replacement in patients with primary MR.

VIEW ON THE NEWS

Francis J. Podbielski, MD, FCCP, comments:

The author provides valuable insight into how the definition of “success” of a procedure can change depending on the approach to the problem. While the gold standard of open mitral valve repair is 1+ regurgitation or less, those promoting percutaneous valve replacement are willing to accept long term 1+ to 2+ regurgitation. New technology and innovation is critical in medicine, provided the results are at least equivalent or superior to the standard techniques.

“There’s never going to be a randomized controlled trial of repair versus replacement; there’s no equipoise there. We all believe that, in primary MR, repair is superior to replacement. There are no data anywhere to suggest the opposite. It’s essentially sacrosanct,” according to the cardiologist.

In contrast, a major randomized trial of surgical repair versus replacement has been conducted in patients with severe secondary MR. This National Institutes of Health–funded study conducted by the Cardiothoracic Surgical Trials Network found no difference in survival between the two groups (N Engl J Med. 2016 Jan 28; 374[4]:344-53). That’s not a surprising result, Dr. Carabello said, since the underlying cause of this type of valve disease is a sick left ventricle. But, since surgical repair entails less morbidity than replacement – and a percutaneous repair with a leaflet-grasping device such as the MitraClip is simpler and safer than a surgical repair – it seems likely that the future treatment for secondary MR will be a percutaneous device, he said.

That future could depend upon the results of the ongoing COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy), in which the MitraClip is being studied as an alternative to surgical repair for significant secondary MR. The MitraClip, which doesn’t entail a concomitant annuloplasty, is currently approved by the Food and Drug Administration only for patients with primary, degenerative mitral regurgitation not amenable to surgical repair. But, if COAPT yields positive results, the role of the MitraClip will greatly expand.

An intriguing and poorly understood difference exists in the significance of residual mitral regurgitation following surgical repair as opposed to percutaneous MitraClip repair, Dr. Carabello observed.

“I go to the OR a lot, and I know of no surgeon [who] will leave 2+ MR behind. Most surgeons won’t leave 1+ MR behind. They’ll put the patient back on the pump to repair even mild residual MR, accepting only trace MR or zero before they leave the OR because they know that the best predictor

of a failed mitral repair is the presence of residual MR in the OR,” he said.

In contrast, following successful deployment of the MitraClip most patients are left with 1-2+ MR. Yet, as was demonstrated in the 5-year results of the randomized EVEREST II trial (Endovascular Valve Edge-to-Edge Repair Study), this residual MR wasn’t a harbinger of poor outcomes long-term (J Am Coll Cardiol. 2015 Dec 29;66[25]:2844-54).

“You would have expected, with that much residual MR, there would be a perpetually increasing failure rate over time, but that didn’t happen. In Everest II, there was an early failure rate for percutaneous repair, where the MitraClip didn’t work and those patients required surgical mitral valve repair. But, after the first 6 months, the failure rate for the clip was exactly the same as the surgical failure rate, even though, with the clip, you start with more MR to begin with,” the cardiologist noted.

The MitraClip procedure is modeled after the surgical Alfieri double-orifice end-to-end stitch technique, which has been shown to have durable results when performed in conjunction with an annuloplasty ring for primary MR.

“The MitraClip essentially joins the valve in the middle the way the Alfieri stitch does, but it doesn’t appear to behave the same way. Why is that? Maybe the clip does something different than the Alfieri stitch on which it was modeled. Maybe that bar in the middle of the mitral valve does something in terms of scarring or stabilization that we don’t know about yet,” he speculated.

As for the prospects for percutaneous mitral valve replacement, Dr. Carabello said that this type of procedure “is a very difficult thing to do, and so far, has been met with a fair amount of failure. It’ll be very interesting to see what percentage of market share it gets 10 years down the road. My prediction is that, for mitral regurgitation, repair is always going to be it.”

Dr. Carabello reported serving on a data safety monitoring board for Edwards Lifesciences.

bjancin@frontlinemedcom.com

Continued from previous page

and more likely to be female than the 824 subjects with an LVEF of 30% or less. They also had a shorter QRS duration – an average of 160 ms, versus 165 ms in patients with an LVEF of 30% or lower – and a smaller baseline left ventricular end systolic volume of 151 mL, compared with 196 mL in patients with a lower LVEF.

In a multivariate Cox regression analysis adjusted for potential confounders, CRT-D in patients with a baseline LVEF greater than 30% was associated with a 54% reduction in the risk of all-cause mortality at 7 years of follow-up, compared with receipt of an ICD-only device and with a smaller yet significant 31% reduction in risk in those with an LVEF of 30% or less. Worsening heart fail-

ure events were reduced by 64% in patients with a baseline LVEF greater than 30% who received CRT-D, compared with ICD-only, and by 54% in those with a lower baseline LVEF.

The reduction in all-cause mortality seen with CRT-D was confined to patients who were high responders to CRT as defined echocardiographically by at least a 35% change in left ventricular end systolic volume 1 year post implantation. They had an 85% reduction in the risk of death during 7 years of follow-up with CRT-D if their baseline LVEF was greater than 30% and a 58% relative risk reduction if their LVEF was 30% or less.

In contrast, CRT-D brought a significantly reduced risk of heart failure events regardless of whether a patient was a low or high responder, although the magnitude of benefit was greater

in the high responders. Among patients with a baseline LVEF greater than 30%, CRT-D low responders had a 52% reduction in risk of heart failure events, compared with ICD recipients, while CRT-D high responders had an 81% relative risk reduction. Similarly, in patients with a baseline LVEF of 30% or less, CRT-D low responders had a 48% reduction in heart failure events and high responders had a 79% risk reduction, compared with the ICD-only group.

Because this is a post hoc analysis, these new MADIT-CRT findings require validation in future studies, Dr. Vermilye observed.

MADIT-CRT was supported by Boston Scientific. Dr. Vermilye reported having no financial conflicts.

bjancin@frontlinemedcom.com



BRUCE JANCIN/FRONTLINE MEDICAL NEWS

Dr. Katherine Vermilye

Clinical Trial Results Matter

Explore the efficacy and safety data at hcp.eliquis.com



NVAF

Indicated to reduce the risk of stroke and systemic embolism in patients with NVAF¹



NVAF: nonvalvular atrial fibrillation.

INDICATIONS

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

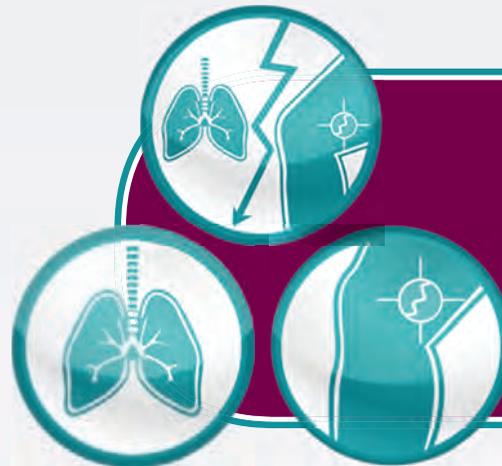
- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition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

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS.



Eliquis[®]

(apixaban) tablets 5mg
2.5mg



DVT/PE

Indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy¹

DVT: deep vein thrombosis;
PE: pulmonary embolism.

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

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

PREGNANCY CATEGORY B

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

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

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

ELIQUIS[®] and the ELIQUIS logo are trademarks of Bristol-Myers Squibb Company.
© 2017 Bristol-Myers Squibb. All rights reserved. 432US1701443-02-01 05/17

ELIQUIS® (apixaban) tablets, for oral use

R ONLY

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

(B) SPINAL/EPIDURAL HEMATOMA

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

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

[see *Warnings and Precautions*]

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

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

INDICATIONS AND USAGE

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

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

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

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

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

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

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

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

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

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

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

Bleeding

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

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

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

Reversal of Anticoagulant Effect

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

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

Spinal/Epidural Anesthesia or Puncture

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

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

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

Patients with Prosthetic Heart Valves

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

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

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

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

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

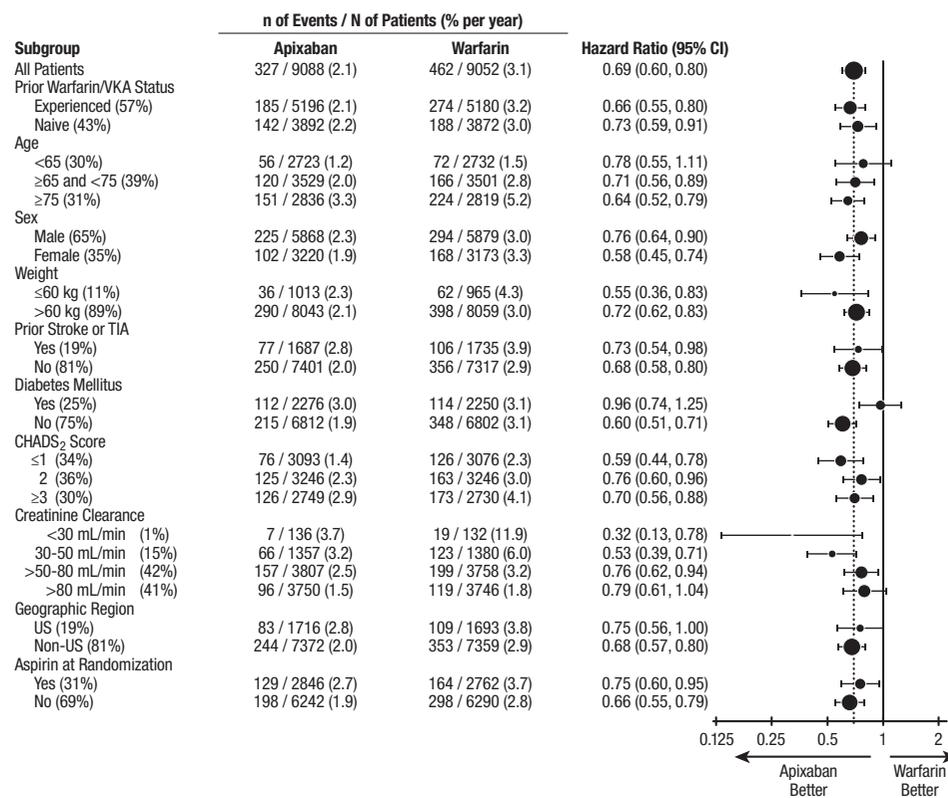
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

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

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

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

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



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

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

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

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

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

Other Adverse Reactions

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days. In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

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

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

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

* All bleeding criteria included surgical site bleeding.
 † Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
 ‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
 § Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
 ¶ CRNM = clinically relevant nonmajor.

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

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

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

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

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

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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

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

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

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

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

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

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

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

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

AMPLIFY Study

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

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

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

Table 5: Bleeding Results in the AMPLIFY Study

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

* CRNM = clinically relevant nonmajor bleeding. Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

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

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

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

AMPLIFY-EXT Study

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

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

Table 7: Bleeding Results in the AMPLIFY-EXT Study

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

* CRNM = clinically relevant nonmajor bleeding. Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

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

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

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

Other Adverse Reactions

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

Blood and lymphatic system disorders: hemorrhagic anemia

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

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

Musculoskeletal and connective tissue disorders: muscle hemorrhage

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

Vascular disorders: hemorrhage

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

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

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

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

DRUG INTERACTIONS

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

Strong Dual Inhibitors of CYP3A4 and P-gp

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

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

Strong Dual Inducers of CYP3A4 and P-gp

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

Anticoagulants and Antiplatelet Agents

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

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

Labor and Delivery

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

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

Nursing Mothers

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Renal Impairment

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

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

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

Patients with End-Stage Renal Disease on Dialysis

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

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

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

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

Hepatic Impairment

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

OVERDOSAGE

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

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

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

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

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

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
and
Pfizer Inc
New York, New York 10017 USA

1356615A2 / 1356514A1

Rev July 2016

432US1603587-13-01

FROM THE EVP/ CEO

BY STEPHEN J. WELCH

It is an incredible honor to be recently confirmed as the EVP/CEO for the CHEST organization. As a 23-year veteran of CHEST, I have had the privilege of working with and for many of our leaders, volunteers, and members. Being only the fifth person to lead the organization in an executive leadership role is both humbling and invigorating. CHEST is a dynamic and innovative organization, with a mission to “champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.” That mission resonates deeply with me on a personal level, because my mother had COPD. Toward the end of her life, I saw firsthand how it impacted her quality of life and her ability to be a mother and grandmother, and I also saw the important role her pulmonologist and respiratory health-care providers played in managing her disease. Working for CHEST reminds me every day of the importance of what we do as an organization in order to support what



MR. WELCH

you do as a physician or advanced practice provider.

I am both fortunate and grateful to have such a phenomenal professional staff to work with here at CHEST and to have the outstanding leadership of our Presidents, Past Presidents, Boards, Committees, and NetWorks – all of which have been tremendously supportive during the past 9 months as I filled the Interim EVP role. I am also deeply grateful to those of you who choose to be members and Fellows of CHEST and

I am both fortunate and grateful to have such a phenomenal professional staff to work with here at CHEST and to have the outstanding leadership of our Presidents, Past Presidents, Boards, Committees, and NetWorks – all of which have been tremendously supportive during the past 9 months as I filled the Interim EVP role. I am also deeply grateful to those of you who choose to be members and Fellows of CHEST and to be engaged as volunteer leadership, faculty, content experts, authors, and more.

to be engaged as volunteer leadership, faculty, content experts, authors, and more. It is your time, energy, involvement, and vision that make this organization what it is. The fact that you choose to give some of your valuable time toward helping CHEST achieve its mission and vision is so greatly appreciated by all of us in this organization. Thank you for all that you do for CHEST.

In recent years, the College has continued to realize the following significant achievements:

1. Growth of our educational programs in simulation, skills training, and procedures;
2. The building and of our new global HQ and Innovation, Simulation, and Training Center;
3. An increasingly global footprint as we deliver education to our physician and advance practice provider members and nonmembers in the US and around the world;
4. Increasing development of digital publications and essential content, such as our journal; CHEST®, CHEST-SEEK™ products, e-learning modules, evidence-based guidelines, and more that can be served up to anyone on any device;
5. Growth and maturation of our CHEST Foundation and its research and service awards;
6. Expansion of patient education initiatives and materials;
7. Development of a data warehouse that will allow us to serve our members and partners more effectively; and
8. Far too many more achievements to list here.

Since taking on the EVP/CEO role, I've been asked what do I consider my primary responsibilities to be. I think this is best summed up by Rick Moyers, in The Nonprofit Chief Executive's Ten Basic Responsibilities (BoardSource, 2006). In it, he outlines the executive's responsibilities as follows:

1. Commit to the mission.
2. Lead the staff and manage the organization.

3. Exercise responsible financial stewardship.
4. Lead and manage fundraising.
5. Follow the highest ethical standards, ensure accountability, and comply with the law.
6. Engage the board in planning and lead the implementation.
7. Develop future leadership.
8. Build external relationships and serve as an advocate.
9. Ensure the quality and effectiveness of programs.
10. Support the board.

These 10 basic responsibilities provide the framework and foundation for how I plan to serve as EVP/CEO of CHEST. In many cases, I've been doing much of this as a senior executive at CHEST for the past 23 years, and I look forward to continuing to build on that foundation.

I am also often asked what my vision for the organization is, as its new EVP/CEO. And my answer is simple: to ensure that the American College of Chest Physicians stays relevant in this environment of change and disruption, that it continues to fulfill its mission, and that members, leadership, volunteers, and staff work together, make a positive impact on patient care, and, ultimately, have fun doing the good work of CHEST. This organization has an outstanding reputation, legacy, and brand. I will do everything I can to maintain and improve upon those key attributes.

It is my ultimate responsibility to ensure that we operationalize the educational programs and activities that align with the strategic plan and achieve the organizational goals of CHEST, which have been set by your Boards and Committees. I look forward to proudly and humbly serving as the CHEST evangelist and advocate to our members, patients, partners, and sister societies. I look forward to hearing from you, our members, about how CHEST is doing, and how we can continue to meet – and exceed – your educational and professional needs.

CHEST® Board Review 2017

Study Smart

Customize your board review study plan with our in-person and on-your-own study tools.



Over **90%** of 2016 CHEST Board Review course attendees would **RECOMMEND** the course to a friend.

Live course registration now open.
Join us in Orlando, August 18-27.

Critical Care Medicine
Board Review
August 18-21

Sleep Medicine
Board Review
August 18-20

Pulmonary Medicine
Board Review
August 23-27

Board Review On Demand

Prep for your board exam, and review the latest recorded content from previously recorded CHEST pulmonary, critical care, sleep, and pediatric pulmonary board review courses.

MOC Assessment and Improvement Modules

Evaluate your current practice, and identify areas for improvement through seven different modules.

CHEST SEEK™ Education

Test your recall, interpretation, and problem-solving skills with case-based questions developed from the content blueprints for the board examinations.

NEW! CHEST SEEK Library Subscription

Stay on top of your practice, challenge your knowledge, and prepare for your board exam with the largest collection of SEEK questions ever offered.

> Learn More boardreview.chestnet.org

Building bridges: CHEST Foundation collaborations

Partnering with like-minded advocates and organizations strengthens our collective voice to improve patient outcomes. We choose to partner with others who share our values in creating sustainable, long-lasting change by engaging clinicians, patients, caregivers, and the public on the importance of understanding lung health.

Pulmonary Fibrosis Foundation

We recently collaborated with the Pulmonary Fibrosis Founda-

tion (PFF) and the Feldman Family to host the *4th Annual Irv Feldman Texas Hold'em and Casino Night* in Deerfield, Illinois. The Irv Feldman Texas



Hold'em and Casino Night was founded by the Feldman Family in 2013 in memory of their father who had succumbed to idiopathic pulmonary

fibrosis (IPF). For the last 4 years, Laury, Mara, and Mitch Feldman have hosted poker and casino nights to raise money to help end pulmonary fibrosis, and this year's event *Continued on following page*

This month in CHEST: Editor's picks

BY RICHARD S. IRWIN, MD,
MASTER FCCP
Editor in Chief, CHEST

GIANTS IN CHEST MEDICINE

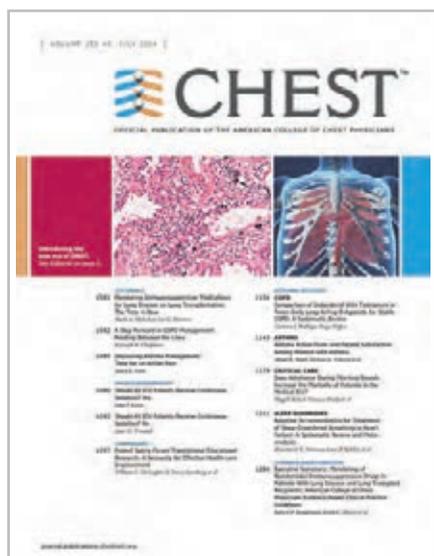
Karlman Wasserman, MD, PhD, FCCP. By Dr. T. Kisaka, et al.

ORIGINAL RESEARCH

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. By Dr. P. Marik, et al.

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial. By Dr. M. H. Kollef, et al.

Quantitative CT Measures of Bronchiectasis in Smokers. By Dr. A. A. Diaz, et al.



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

SLOW THE PATH OF IPF PROGRESSION

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

DISCOVER MORE ABOUT OFEV INSIDE.

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS
Hepatic Impairment

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

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
FVC, forced vital capacity.

TREAT NOW. SLOW PROGRESSION.

Continued from previous page

featured a poker tournament, silent auction, dinner buffet, and live entertainment. This local community-based support resulted in almost \$200,000 raised at the poker night to fight against pulmonary fibrosis. In collaboration with the Pulmonary Fibrosis Foundation,

these proceeds will support pulmonary fibrosis patient education, disease awareness, and clinical research. We thank the Feldman Family and the Pulmonary Fibrosis Foundation for making this successful event possible.

Allergy & Asthma Network

Over the past 2 years, our relationship

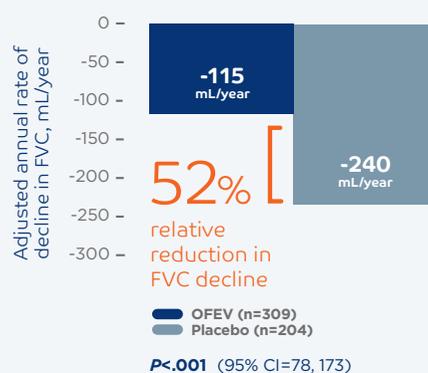
with the Allergy & Asthma Network (AAN) has grown to include collaborative disease awareness campaigns, co-branded and co-created patient education materials in asthma and COPD, and an exciting expansion of the platforms we utilize to reach patients. Partnering with the AAN has allowed us to reach new audiences and bring asthma

and COPD education to local communities with opportunities, including:

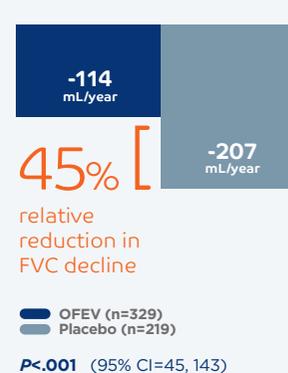
- A Lifetime television segment on Access Health that focuses on asthma education;
- Co-hosted asthma Twitter chats reaching thousands of clinicians and patients; and
- “The Air We Breathe,” an Atlantic

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

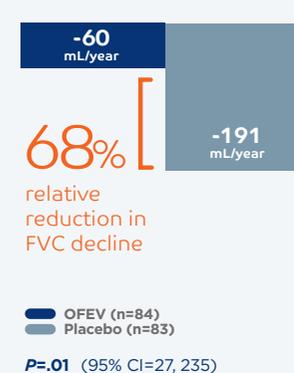
INPULSIS[®]-1 (Study 2)^{3,4}



INPULSIS[®]-2 (Study 3)^{3,4}



TOMORROW (Study 1)^{3,5}



CI, confidence interval.

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes

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

Gastrointestinal Disorders

Diarrhea

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

Nausea and Vomiting

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

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



ONE CAPSULE,
TWICE DAILY WITH FOOD³

Not shown at actual size

Live Summit in Chicago which focused on the relationship between air quality and respiratory health.

COPD Foundation

The COPD Foundation, along with Allergy & Asthma Network, have partnered with us to support our Lung Health Experience, a lung

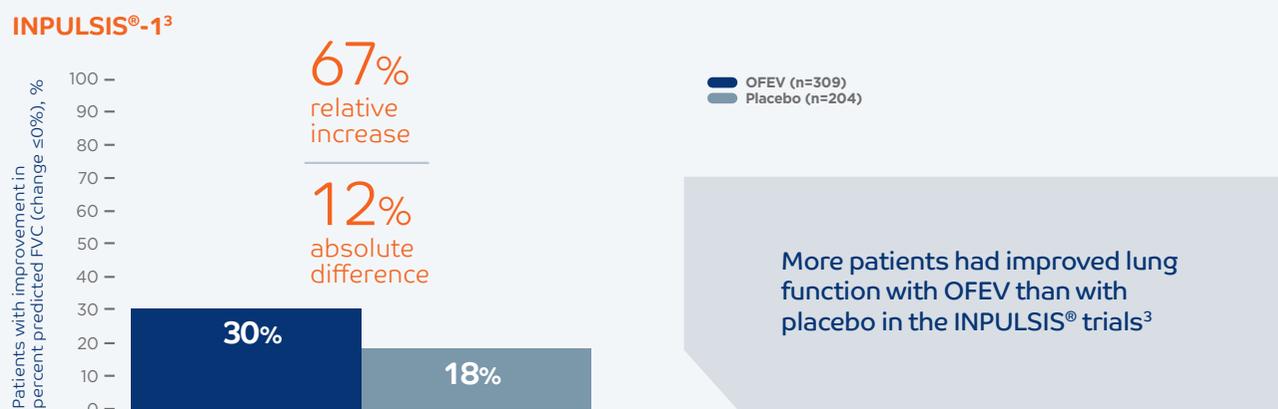
health expo touring Oklahoma City, Nashville, Chicago, and Toronto in 2017. The Lung Health Experience focuses on bringing lung health experts to the public in a comfortable, relaxed, and fun setting. The COPD Foundation and AAN have attended these events to provide the public with educational materials on lung

diseases, which support the spirometry screenings performed by local respiratory therapists. We thank the Allergy & Asthma Network and the COPD Foundation for their outstanding support.

It is with these and many other partnerships that the CHEST Foundation is able to elevate its mission to

champion lung health and provide local communities with an opportunity to interact with clinicians and physicians outside of a hospital setting. These experiences and collaborations are the key to strengthening the patient and clinician conversation and bridging the gap to improve patient care and outcomes.

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



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

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



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

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



Low payment for pulmonary rehab explained

BY PHIL PORTE
Executive Director, NAMDRC

A new review of 2015 Medicare data clearly points fingers at hospitals for the historically low

payment rates for pulmonary rehabilitation.

To fully understand these data, everyone involved in the delivery of pulmonary rehabilitation services needs to know some of the specifics regarding

Medicare's rate setting process for hospital outpatient services. Those services are paid on the basis of a prospective payment methodology, similar to the DRG system for inpatient services. Under the outpatient system, APCs (am-

bulatory payment classifications) are computed with two key data sources, both provided by hospitals.

First, every claim submitted to Medicare for an outpatient service must include the hospital's "charge"

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.



Copyright ©2016, Boehringer Ingelheim Pharmaceuticals, Inc. All rights reserved. (06/16) PC-OF-0473-PROF



for the service. (IMPORTANT NOTE: It is very easy to use the terms cost, charge, payment, and reimbursement interchangeably, but when discussing this issue, it is critically important to make key distinctions). This “charge” is not what the hospital expects to get paid – it is information from the hospital’s

Knowing some of the specifics regarding Medicare’s rate setting process for hospital outpatient services is necessary in order to fully understand these data.

“chargemaster” that identifies what, in theory, a self-pay patient might pay for a certain service. Therefore, every claim submitted to CMS for payment

of code **G0424** (pulmonary rehabilitation services) must include this “charge” data.

The second key component used

by CMS for rate setting is the hospital cost report, submitted annually to CMS tied to the individual hospital’s fiscal year. This flow of data to CMS is ongoing because of differing fiscal years and is somewhat attributable to changes in Medicare proposed rates for the following year, published in

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

July, compared with final rates, published in early November.

The other key historical fact that needs emphasis is what happened in 2010 when CMS began reimbursing for pulmonary rehab under new HCPCS code **G0424**. Clearly, there were no

charge data to examine, so the Agency had to do a bit of guesswork, estimating what would be a reasonable payment. CMS turned to payment information tied to codes **G0237** and **G0238**, codes that had been used by many institutions for the previous decade for billing pulmonary rehab. But one critical difference existed. The

new code, **G0424**, was a 1-hour code, while **G0237-38** were 15-minute codes. Over the next 2 years, even CMS cited the failure of hospitals to adjust their charges to reflect all the component services included in this new, bundled 1-hour code, compared with the unbundled 15-minute code.

The new review of CMS data

bears out this problem. With approximately 1,350 institutions billing for hospital outpatient pulmonary rehab via code **G0424**, there is incredibly wide variance in charge data. The range is from a high of \$1,981 to a low of \$44, with 1,350 institutions in-between. The average charge was \$247, but the difference between the lowest charge and the highest charge is approximately 44-fold.

For cost report data, the spread is from \$1,265 to \$4 (yes, \$4, based on data provided to CMS). Approximately 750 hospitals, more than half, submit data to CMS reflecting costs associated with the delivery of pulmonary rehab, per hour, at \$50 or less.



MR. PORTE

There are probably several reasons why hospitals behave this way. First, there is the historical phenomenon cited by CMS that it often takes years for hospitals to adjust charges appropriately when any new HCPCS code is adopted by CMS. And, in fact, CMS cited pulmonary rehab as a glaring example of that failure by hospitals. Second, there is the cost report data, and we believe it, too, falls victim to hospital neglect. We can understand that a service such as pulmonary rehab falls so far below the radar by chargemasters, hospital administrators and others associated with information submitted to CMS that little attention is paid to accuracy of charges or administrative costs culled from the hospital cost report. And then, there is the matter of community relations. The hospitals at the very high end of the spectrum in terms of charges (\$1,100 and up) are unlikely to build good community relations if they let people know of those charges. Ironically, it is fair to presume that hospitals do pay very close attention to their charges and cost report data for very high-end hospital outpatient services, micro-examining that information to ensure desirable payment rates.

So, the critical challenge to the pulmonary community is to focus on those two very specific bits of data submitted by hospitals to CMS: what a hospital identifies as the “charge” for code **G0424** and is then entered on every claim submitted to **G0424**; and second, information correlated to the administrative aspects of pulmonary rehab that hospitals submit to CMS annually in their cost report to CMS. Until those adjustments are made, pulmonary rehab will live with unacceptable payment rates.

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].

Copyright © 2016 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

OF-BS-2-16 (2-16) PC-OF-0365-PROF

Rx only



SPECIAL REPORT RELEASED BY FIRS

The Global Impact of Respiratory Disease – Second Edition

The Global Impact of Respiratory Disease – Second Edition was released by the Forum of International Respiratory Societies (FIRS) at the World Health Assembly May 25, 2017, in Geneva, Switzerland, calling attention to the global burden of lung disease and the benefits of prevention and clean air.

We often take our breathing and our respiratory health for granted, but respiratory diseases are a leading cause of death and disability in the world. Sixty-five million people suffer from COPD, and 3 million die of it each year, now making it the third leading cause of death worldwide.^{1,2} Asthma affects 334 million people in the world and is the most common chronic disease of childhood.³ Pneumonia kills millions of people annually and is a leading cause of death among children under 5 years old.⁴ Over 10 million people develop TB, and 1.4 million die of it each year, making it the most common deadly infectious disease.⁵ Lung cancer kills 1.6 million people each year and is the most deadly cancer.⁶ Globally, at

least 2 billion people are exposed to indoor toxic smoke, 1 billion inhale outdoor pollutant air, and 1 billion are exposed to tobacco smoke. Many

We often take our breathing and our respiratory health for granted, but respiratory diseases are a leading cause of death and disability in the world.

of us, and the world, are naïve to these staggering realities.

The American College of Chest Physicians® (CHEST), together with FIRS, is working hard to change these realities. CHEST, and our more than 19,000 members around the world, want a better future, one that has less suffering. We want a future that enables and allows everyone to breathe freely.

The 2017 Global Impact of Respiratory Disease report objectively speaks to these issues and outlines an

eight-step action plan to impact these serious concerns. It highlights the importance of prevention, control, and cure of these diseases and announces that promotion of respiratory health must be a top priority for health-care systems and decision-makers. In emphasizing that these goals are achievable, it also highlights the reality that the prevention and cure of respiratory diseases are among the most cost-effective health interventions available – a “best-buy” in the view of the World Health Organization (WHO). In addition to reducing so much suffering, investment in respiratory health will pay manifold dividends in longevity, healthy living days, and national economies.

Darcy Marciniuk, MD, FCCP, FRCPC, and Co-Chair of the Report notes, “The Global Impact of Respiratory Disease” report calls attention to the importance of respiratory health in the world. The report and these efforts are required to ensure respiratory health becomes a top priority in global decision-making.”

In addition to focusing attention to

the importance of respiratory health in the world and ensuring it becomes a global priority, the 2017 Global Impact of Respiratory Disease report also includes practical information for our members. The report summarizes the current state of our understanding with the “Big 5”: COPD, asthma, pneumonia, lung cancer, and TB, as well as with the environment and clean air, sleep-disordered breathing, pulmonary hypertension, and pulmonary embolism. It highlights key controllable factors, such as a reduction in tobacco smoking and improvement in air quality, which includes reduction in second-hand tobacco smoke, smoke from indoor fire, and unhealthy public and workplace air. The report underlines the value of trained health-care professionals and the need for health-care systems and policies to support those trained professionals. Finally, it emphasizes the reality that investment in respiratory research is more than the hope for today – it is the promise and a genuine commitment for tomorrow.

Continued on following page

Cardiopulmonary Exercise Testing (CPET)

September 22-24



Prominent national and international exercise experts guide you through didactic and hands-on sessions about high-level interpretive strategies you can use to better support your exercise laboratory.

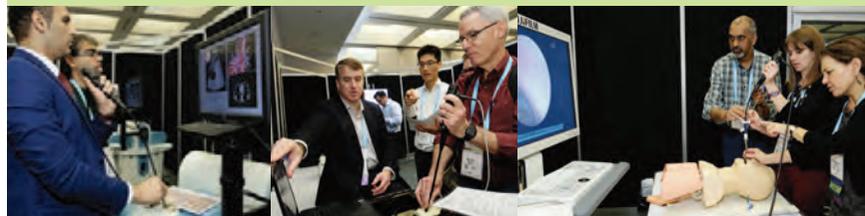
Gain practical experience with:

- Necessary technical aspects of the CPET equipment
- The skills required for performing CPET, including calibration, maneuvers, testing, and biologic controls
- Data interpretation, including report creation and how to make informed CPET study recommendations

Target Audience Pulmonary physicians; pulmonary function testing and cardiology laboratory directors; advanced practice providers; family medicine, critical care, and pulmonary rehabilitation providers; pulmonary fellows; internists; hospitalists; exercise physiologists; CPET laboratory medical directors; and cardiologists are encouraged to attend.

> Learn More chestnet.org/live-learning

CHEST Innovation, Simulation, and Training Center • Glenview, Illinois



Advance Your Bronchoscopy Skills

Improve key bronchoscopy and procedure-related skills with our 2017 live, in-person courses. Gain hands-on experience in a wide variety of relevant procedures ranging from conventional and EBUS-guided TBNA, to bronchoscopy-guided percutaneous tracheostomy, to tunneled indwelling pleural catheter placement. All courses feature interactive, small-group settings led by content experts.

Pulmonary and critical care fellows, physicians, intensivists, thoracic surgeons, and advanced practice providers are encouraged to attend.

Comprehensive Pleural Procedures

August 4-5

CME credits and MOC points: 15.00

Key topics: Ultrasound-guided thoracentesis, pleural manometry, tunneled indwelling pleural catheter placement, small bore and standard thoracostomy tube placement, and flex-rigid pleuroscopy for pleural effusion diagnosis

Comprehensive Bronchoscopy With Endobronchial Ultrasound

September 29-October 1

CME credits and MOC points: 21.00

Key topics: Biopsy, brushings, conventional and EBUS-guided TBNA, radial EBUS for peripheral nodules, management of airway bleeding and aspirated foreign objects, and lung cancer diagnosis and staging strategies



Learn More livelearning.chestnet.org/bronchoscopy

ABIM Internal Medicine Summit

BY HEATHER DETHLOFF, MA
CHEST Education and Accreditation Manager

On April 7, four members of CHEST staff and leadership, along with staff and leadership from other medical specialty societies, participated in the Internal Medicine Summit, hosted by the American Board of Internal Medicine, in Philadelphia. The meeting covered an array of topics related to

Continued from previous page

CHEST's involvement in this important project is only one component of our global engagement and impact. We support and help to educate lung specialists and health-care teams, no matter where they live and work. Our journal *CHEST*®, and other education offerings, are used every day and in every part of the world. The American College of Chest Physicians® focuses on the prevention, diagnosis, and treatment of chest diseases by providing innovative education and advancing best patient outcomes around the globe.

About the Forum of International Respiratory Societies (FIRS) Formed in 2001, the Forum of International Respiratory Societies (FIRS) is composed of the leading international respiratory societies, with more than 70,000 members who devote their working lives to respiratory health and disease. The goal of FIRS is to speak with one voice in promoting respiratory health worldwide and to call for action to reduce, prevent, cure, and control the terrible burden of respiratory disease.

References

1. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases, a comprehensive approach. 2007.
2. Burney PG, Patel J, Newson R, et al. Global and regional trends in COPD mortality, 1990-2010. *Eur Respir J*. 2015;45(5):1239-47.
3. International Study of Asthma and Allergies in Childhood (ISAAC). Global Asthma Report. 2014.
4. World Health Organization. Pneumonia: the forgotten killer of children. Geneva: World Health Organization; 2006.
5. World Health Organization. Global Tuberculosis Report 2016. Geneva: World Health Organization; 2016.
6. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.

certification and maintenance of certification (MOC), including the alternative assessment model announced in December 2016, quality improvement (QI) as part of MOC, and practicing medicine in an ever-changing

political landscape.

The meeting began with Dr. Richard Baron, President and CEO of the ABIM, explaining how the notion of certification has changed over the years. According to Dr. Baron, the

concept of lifetime certification no longer makes sense in the rapidly changing field of medicine. As part of the evolution of certification, the ABIM has moved away from "rules to follow" toward something, co-created

**orenitram[®]
treprostiniil**
EXTENDED-RELEASE TABLETS
For pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity

TYVASO[®]
(treprostiniil) INHALATION SOLUTION

For the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability

REMODULIN[®]
(treprostiniil) Injection

For the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise

**orenitram[®]
treprostiniil**
EXTENDED-RELEASE TABLETS

FC=functional class; PAH=pulmonary arterial hypertension; WHO=World Health Organization.

References: 1. McLaughlin et al. ACCF/AHA 2009 expert consensus on pulmonary hypertension: developed in collaboration with the ACCP, ATS, and the PHA. *J Am Coll Cardiol*. 2009;53(17):1573-1619. 2. Orenitram [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2016. 3. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2016. 4. Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2014. 5. Guidepoint Global, LLC. 40 PAH centers surveyed, last verified October 2016.

with societies, that is more relevant and less burdensome. This shift includes aligning certification and MOC requirements with things physicians are already required to do by their states and institutions. Dr. Baron also stressed that in today's cultural and political landscape, along with the prevalence of "fake news," the

need for trust in the doctor-patient relationship is increasing; trust is no longer a "given." Therefore, in an age when credentials can be purchased online, there's an increasing need for an external certification to build trust and boost credibility.

Dr. Marianne Green, member of the ABIM Board of Directors and the

ABIM Council, gave an update on the recertification assessment options. While currently, only an every 2-year assessment option will be offered as an alternative to a 10-year higher stakes exam, the ABIM is looking to partner with societies to deliver education, based on the needs identified via the assessment. Furthermore, in

addition to partnering with societies to address the identified knowledge gaps, the ABIM plans to collaborate with societies in future alternatives to both the 2-year and 10-year assessments, with the shared goal of "maintenance and support of a community of life-long learners who hold

Continued on following page

TREATING PAH IS A MATTER OF URGENCY.¹ WHY WAIT TO INITIATE A PROSTACYCLIN ANALOGUE?

CULTIVATE A CONTINUUM OF CARE WITH THE TREPHESTINIL SYSTEM

A range of prostacyclin analogues for cohesive PAH treatment over the course of disease.²⁻⁴

START ORENITRAM EARLY—AT FC II OR III²

The only prostacyclin analogue in a tablet is the adaptable foundation of the treprostiniil system²

- **Turn to Tyvaso**—for direct-to-the-lungs, inhaled delivery when patients require a different administration route³
- **Reach for Remodulin**—for the #1-prescribed parenteral PAH therapy⁵
- **Return to Orenitram**—for oral delivery in hemodynamically stable FC I and II Remodulin patients²

Talk to your United Therapeutics representative for more information.

SELECTED IMPORTANT SAFETY INFORMATION FOR TREPHESTINIL

- Treprostiniil is a pulmonary and systemic vasodilator. Concomitant administration of treprostiniil with blood pressure lowering agents, such as diuretics, antihypertensive agents, or other vasodilators, may increase the risk of symptomatic hypotension
- In patients with hepatic impairment, there is an increase in systemic exposure to treprostiniil relative to patients with normal hepatic function; therefore, treprostiniil dosage should be titrated slowly in these patients

- Abrupt discontinuation of treprostiniil, or sudden large reductions in dosage, may result in worsening of PAH symptoms
- Treprostiniil inhibits platelet aggregation and increases the risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of treprostiniil and a CYP2C8 inhibitor, such as gemfibrozil, increases exposure to treprostiniil; therefore, treprostiniil dosage reduction may be needed in these patients
- Some common adverse reactions of treprostiniil include headache, nausea and flushing

Please see the complete Important Safety Information for each product on next page and the Brief Summaries of the Full Prescribing Information for each product on subsequent pages.

Orenitram, Remodulin, and Tyvaso are registered trademarks of United Therapeutics Corporation. All other registered trademarks are the property of their respective owners. The makers of these brands are not affiliated with and do not endorse United Therapeutics or its products. © 2017 United Therapeutics Corporation. All rights reserved. US/RTO/0026 Printed in USA.

 **United
Therapeutics**
CORPORATION
COMMITTED TO PAH

Continued from previous page

ourselves accountable to peer-defined standards." Initially, the 2-year lower stakes assessment will cover the breadth of the knowledge in the specialty/subspecialty, but the ABIM is committed to taking a more modular approach in the future. When asked

about the fee structure for the new assessment options, Dr. Green communicated that details regarding fees would be announced in fall 2017.

While the first part of the meeting focused on MOC Part 2, the conversation turned toward quality improvement, or QI, later part of the meeting. The practice improvement,

or MOC Part 4, requirement is on hold through the end of 2018. Both the ABIM and represented societies value the importance of quality measures. Dr. Graham McMahon, president and CEO of Accreditation Council for Continuing Medical Education (ACCME), laid the framework for QI as being "activities that address

a quality or safety gap with interventions intended to result in improvement and with specific, measurable goals. QI activities are learner-driven, as learner engagement is a key target of ACCME's standard. Representatives from the Heart Rhythm Society, the Society of Hospital Medicine, the Arthritis Foundation, and the American

ORENITRAM® (treprostinil) EXTENDED-RELEASE TABLETS

Indication

Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

Important Safety Information for Orenitram

Contraindications

- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

Warnings and Precautions

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum

Drug Interactions / Specific Populations

- Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
- Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
- Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans
- It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding
- Safety and effectiveness in patients under 18 years of age have not been established
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

Adverse Reactions

- In the 12-week placebo-controlled monotherapy study, adverse reactions that occurred at rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

OREIShpcJAN16

TYVASO® (treprostinil) INHALATION SOLUTION

Indication

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

Important Safety Information for Tyvaso

Warnings and Precautions

- The efficacy of Tyvaso has not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- Tyvaso is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension.
- Titrate slowly in patients with hepatic or renal insufficiency, as exposure to treprostinil may be increased in these patients.
- Tyvaso inhibits platelet aggregation and increases the risk of bleeding, particularly in patients receiving anticoagulants.
- Co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil may increase exposure to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events, whereas decreased exposure is likely to reduce clinical effectiveness.

Drug Interactions / Specific Populations

- The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Co-administration of the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to *oral treprostinil*. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to *oral treprostinil*. It is unclear if the safety and efficacy of *treprostinil by the inhalation* route are altered by inhibitors or inducers of CYP2C8.
- There are no adequate and well-controlled studies with Tyvaso in pregnant women. It is not known whether treprostinil is excreted in human milk.

Adverse Reactions

- The most common adverse events seen with Tyvaso in $\geq 4\%$ of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/ pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%).

TYVISIhpcJUN16

REMODULIN® (treprostinil) INJECTION

Indication

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with

chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route or in whom these risks are considered warranted.

In patients with PAH requiring transition from Flolan® (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Important Safety Information for Remodulin

Warnings and Precautions

- Chronic intravenous (IV) infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSI) and sepsis, which may be fatal. Therefore, continuous subcutaneous (SC) infusion is the preferred mode of administration.
- Avoid abrupt withdrawal or sudden large reductions in dosage of Remodulin, which may result in worsening of PAH symptoms.
- Titrate slowly in patients with hepatic or renal insufficiency because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.
- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. Co-administration of Remodulin with a CYP2C8 inhibitor increases exposure to treprostinil, or with an inducer, decreases exposure to treprostinil.

Drug Interactions/Specific Populations

- Remodulin is a potent pulmonary and systemic vasodilator. Concomitant administration of Remodulin with blood pressure lowering agents, such as diuretics, antihypertensive agents, or other vasodilators, may increase the risk of symptomatic hypotension.
- Since Remodulin inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.
- Safety and effectiveness of Remodulin in pediatric patients have not been established. It is unknown if geriatric patients respond differently than younger patients. Caution should be used when selecting a dose for geriatric patients.
- There are no adequate and well-controlled studies with Remodulin in pregnant women. It is not known whether treprostinil is excreted in human milk.

Adverse Reactions

- Adverse Reactions:** In clinical studies of SC Remodulin infusion, the most common adverse events reported were infusion site pain and infusion site reaction (redness and swelling). These symptoms were often severe and sometimes required treatment with narcotics or discontinuation of Remodulin. The IV infusion of Remodulin has been associated with a risk of blood stream infections, arm swelling, paresthesias, hematoma, and pain. Other common adverse events ($\geq 3\%$ more than placebo) seen with either SC or IV Remodulin were headache, diarrhea, nausea, jaw pain, vasodilatation, and edema.

Please see the Brief Summary of the Full Prescribing Information for Orenitram on the adjacent page and the Brief Summaries for Tyvaso and Remodulin on the subsequent pages.

College of Rheumatology shared their organization's initiatives related to QI.

Apart from the focus on certification and MOC, the meeting also focused on the needs arising from a changing political world, including what is at stake with the repeal of the Affordable Care Act (ACA) and the challenges arising with the wide

dissemination of questionable news and the general disregard of science. Stephen Welch, CHEST EVP/CEO, participated in a panel entitled "Practicing Medicine in a Fact-Free World." He, along with other media professionals, discussed the challenges that physicians, patients, and physician educators encounter in a

time when false facts are published as truth and information is sensationalized to attract more attention.

Since the meeting, CHEST leadership sent a letter to the ABIM leadership noting a desire to be one of the societies with whom the ABIM collaborates for both alternative assessment methods and the open-book resources

selected. Additionally, CHEST expressed interest in receiving the data that are culled from the assessments, an interest aligned with CHEST's current data analytics initiatives. CHEST will continue to collaborate with the ABIM to ensure CHEST members' needs are represented and prioritized in future discussions.



BRIEF SUMMARY

The following is a brief summary of the full prescribing information for Orenitram® (treprostinil) Extended-Release Tablets. Please review the full prescribing information before prescribing Orenitram.

INDICATIONS AND USAGE

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS

Worsening PAH Symptoms upon Abrupt

Withdrawal—Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

Risk of Bleeding—Orenitram inhibits platelet aggregation and increases the risk of bleeding.

Use in Patients with Blind-end Pouches—The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

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 clinical practice. In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, diarrhea, nausea and flushing. Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least a year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

The safety of Orenitram was also evaluated in an open-label study transitioning patients from Remodulin. The safety profile during this study was similar to that observed in the three pivotal studies.

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

Reaction	Treatment (%)	
	Orenitram (N=151)	Placebo (N=77)
Headache	63%	19%
Diarrhea	30%	16%
Nausea	30%	18%
Flushing	15%	6%
Pain in jaw	11%	4%
Pain in extremity	14%	8%
Hypokalemia	9%	3%
Abdominal discomfort	6%	0%

Post-Marketing Experience—The following adverse reactions have been identified during post approval use of Orenitram: dizziness, dyspepsia, vomiting, myalgia, and arthralgia. 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.

DRUG INTERACTIONS

Antihypertensive Agents or Other Vasodilators—Concomitant administration of Orenitram with diuretics, antihypertensive agents or other vasodilators increases the risk of symptomatic hypotension.

Anticoagulants—Treprostinil inhibits platelet aggregation; there is increased risk of bleeding, particularly among patients receiving anticoagulants.

Effect of CYP2C8 Inhibitors—Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil in healthy adult volunteers increases exposure to treprostinil. Reduce the starting dose of Orenitram to 0.125 mg BID and use 0.125 mg BID increments every 3 to 4 days.

Effect of Other Drugs on Orenitram—Based on human pharmacokinetic studies, no dose adjustment of Orenitram is recommended when co-administered with either fluconazole, rifampin, sildenafil, bosentan or esomeprazole.

Warfarin—A drug interaction study was carried out with Remodulin co-administered with warfarin (25 mg/day) in healthy volunteers. There was no clinically significant effect of either medication on the pharmacokinetics of treprostinil. Additionally, treprostinil did not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the international normalized ratio (INR) in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—*Pregnancy Category C*. Animal reproductive studies with treprostinil diolamine have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans.

Labor and Delivery—The effect of Orenitram on labor and delivery in humans is unknown. No treprostinil treatment-related effects on labor and delivery were seen in animal studies.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Clinical studies of Orenitram did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment—Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure. Titrate slowly in patients with hepatic insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C).

Patients with Renal Impairment—No dose adjustments are required in patients with renal impairment. Orenitram is not removed by dialysis.

OVERDOSAGE

Signs and symptoms of overdose with Orenitram during clinical trials reflect its dose-limiting pharmacologic effects and include severe headache, nausea, vomiting, diarrhea, and hypotension. Treat supportively.

PULMONARY PERSPECTIVES® China's Pulmonary Crisis

BY FRASER MACKAY, MD; AND
ERIC FLENAUGH, MD, FCCP

Over the past 2 years, we had the opportunity to participate in an annual cross-cultur-

al exchange that has broadened our horizons. Xi'an, the ancient capital of China and home of the Terracotta warriors, is a sprawling megapolis similar to Los Angeles. In the southern suburb of Huxian,

US trained pulmonary, neurosurgical, and critical care physicians from Cooper University Hospital and Morehouse School of Medicine partnered with physicians of Ji-Ren Teaching Hospital to deliver a Chi-

nese Medical Association accredited continuing medical education conference. The conference agenda included a variety of pulmonary and critical care topics highlighting sepsis, neurovascular disease, and lung



BRIEF SUMMARY

The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) Inhalation Solution. Please review the full prescribing information prior to prescribing TYVASO.

INDICATIONS AND USAGE

TYVASO is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Patients with Pulmonary Disease or Pulmonary Infections—The efficacy of TYVASO has not been established in patients with significant underlying lung disease (eg, asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Risk of Bleeding—TYVASO inhibits platelet aggregation and increases risk of bleeding.

Effect of Other Drugs on Treprostinil—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (eg, gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (eg, rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions:

- Decrease in systemic blood pressure
- Bleeding

Adverse Reactions Identified in Clinical Trials—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. In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache; gastrointestinal effects; muscle, jaw, or bone pain; flushing; and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years with a maximum exposure of 5.4 years. Eighty-nine percent (89%) of patients achieved the target dose of nine breaths, four times daily. Forty-two percent (42%) achieved a dose of 12 breaths, four times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week, placebo-controlled trial. In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

Adverse Event	Treatment n (%)	
	TYVASO n = 115	Placebo n = 120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation/ Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

(16.2 per 100 patient-years vs. 10.9 per 100 pt-years), throat irritation (4.5 per 100 pt-years vs. 1.2 per 100 pt-years), nasal discomfort (2.6 per 100 pt-years vs. 1.3 per 100 pt-years), and hemoptysis (2.5 per 100 pt-years vs. 1.3 per 100 pt-years) compared to the control group.

Adverse Events Associated with Route of Administration—Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis, and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 15 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

Adverse Reactions Identified in Post-Marketing Experience—The following adverse reaction has been identified during the post-approval use of Tyvaso. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure: Angioedema.

DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diolamine) and subcutaneously administered treprostinil (Remodulin®).

Pharmacodynamics—Antihypertensive Agents or Other Vasodilators—Concomitant administration of TYVASO with diuretics, antihypertensive agents, or other vasodilators may increase the risk of symptomatic hypotension. **Anticoagulants**—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics—Bosentan—In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed. **Sildenafil**—In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed. **Effect of Cytochrome P450 Inhibitors and Inducers**—*In vitro* studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A. Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8. **Effect of Other Drugs on Treprostinil**—Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and flucanazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil.

Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B—There are no adequate and well-controlled studies with TYVASO in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (SC) infusions of treprostinil sodium at infusion rates higher than the recommended human SC infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Also, a study in pregnant rabbits administered oral treprostinil diolamine at exposures higher than those in humans resulted in external fetal and soft tissue malformations and fetal skeletal malformations. Animal reproduction studies are not always predictive of human response.

Labor and Delivery—No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Geriatric Use—Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency—Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency—No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites, and consequently dose-related adverse outcomes may be more frequent.

OVERDOSAGE

In general, symptoms of overdose with TYVASO include: flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

Manufactured for: United Therapeutics Corporation, Research Triangle Park, NC 27709
Reference: 1. TYVASO full Prescribing Information. United Therapeutics Corporation. June 2016.
Rx only
www.tyvaso.com
TYVBSHcpJun16



cancer screening and diagnosis. We also provided a hands-on workshop for point of care ultrasound, and, in return, received education about Chinese medicine.

We found our hosts appreciative and hospitable, and they treated us with the highest level of respect (the cornerstone of Chinese culture).

The audience was receptive and very interested in learning. However, while we were impressed with their rapid growth and interest in incorporating western medicine into their daily practice, it was impossible to overlook the major pulmonary health-care concerns threatening their communities. Tobacco use was

omnipresent, and the haze of air pollution made the sky a constant shade of grey. In both public and private spaces, powerful echoes of a once familiar America resonated, and they served to underscore the obstacles the Chinese medical community now faces in caring for their country's pulmonary health.



DR. MACKAY



DR. FLENAUGH

REMODULIN[®] (treprostinil) Injection

BRIEF SUMMARY

The following is a brief summary of the full prescribing information for Remodulin[®] (treprostinil) Injection, for subcutaneous or intravenous use. Please review the full prescribing information before prescribing Remodulin.

INDICATIONS AND USAGE

Remodulin is a prostacyclin vasodilator indicated for:

- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), reserve continuous intravenous infusion for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.
- Patients who require transition from Flolan[®], to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risk of Catheter-Related Bloodstream Infection—Chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. Continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

Worsening PAH upon Abrupt Withdrawal or Sudden Large Dose Reduction—Avoid abrupt withdrawal or sudden large reductions in dosage of Remodulin, which may result in worsening of PAH symptoms.

Patients with Hepatic or Renal Insufficiency—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Effect of Other Drugs on Treprostinil—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) decreases exposure to treprostinil.

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. Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). Infusion site pain and reaction were the most common adverse events among those treated with Remodulin as a subcutaneous infusion. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration, or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA [†]	NA [†]	1	32
Leading to discontinuation	0	3	0	7

*Based on prescriptions for narcotics, not actual use

[†]Medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Adverse Reactions During Chronic Dosing—Table 2 lists adverse reactions defined by a rate of at least 3% more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Adverse Reaction	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Edema	9	3

The safety of Remodulin was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min). The safety profile during this chronic dosing study was similar to that observed in the 12-week, placebo-controlled study except for the following suspected adverse drug reactions (occurring in at least 3% of patients): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain.

Adverse Events Attributable to the Drug Delivery System—In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem. In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, paresthesias, hematoma, and pain.

Post-Marketing Experience—In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events include thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia bone pain, pruritus, and dizziness. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

DRUG INTERACTIONS

Antihypertensive Agents or Other Vasodilators—Concomitant administration of Remodulin with diuretics, antihypertensive agents, or other vasodilators may increase the risk of symptomatic hypotension.

Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Effect of CYP2C8 Inhibitors and Inducers—Co-administration of Remodulin and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil. Co-administration of Remodulin and the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by parenteral routes are altered by inhibitors or inducers of CYP2C8.

Effect of Other Drugs on Treprostinil—Based on human pharmacokinetic studies, no clinically significant effect on the pharmacokinetics of Remodulin was observed when co-administered with acetaminophen, warfarin, or fluconazole in healthy volunteers.

USE IN SPECIFIC POPULATIONS

Pregnancy Category B—Animal reproductive studies have indicated effects limited to an increase in incidence of fetal skeletal variations. There are no adequate and well-controlled studies in humans.

Labor and Delivery—The effect of Remodulin on labor and delivery in humans is unknown. No treatment-related effects were seen in animal studies.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—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 Insufficiency—Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight, and monitor closely. Remodulin has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency—No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given.

OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

An Old, Familiar Foe

The China National Tobacco Corporation (CNTC) is the largest tobacco company in the world, as well as China's most profitable state-owned enterprise (Pratt, A, et al. WHO Report. 2017. ISBN 9789290617907 [http://www.wpro.who.int/china/publications/2017_china_tobacco_control_report_en_web_final.pdf?ua=1]). As such, the CNTC controls every aspect of its production and supply chain with the force of the federal government and also exerts heavy influence over regulatory policy. It controls about 98% of domestic crop production and manages to price cigarettes just short of one American dollar per pack, yet contributes about \$170 billion annually to the government (Rich, et al. *Nicotine Tob Res.* 2012;14[3]:258). This accounted for nearly 7% of total governmental revenue in 2015 (Pratt, 2017).

To date, nearly 44% of the world's cigarettes are manufactured and consumed in China (Pratt 2017, Rich 2012). In 2015, more than 315 million Chinese adults were daily smokers, or about 28% of the adult population and nearly half of all men (Pratt, 2017). This is about double the proportion of US smokers (about 15.1%) and more than eight times the 36.5 million daily smokers in the United States (CDC Online Tobacco Use Report, 2016 [https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/]). However, to visit China is not only to know a love for tobacco, but also an overwhelming guest and gift culture. Gift giving and hospitality is central to the Chinese identity, from business meetings to afternoon tea. Given their economy and such rich supply, people gift cigarettes to one another at all times for nearly any occasion. Unfortunately, tobacco smoke in China is as inescapable as its health consequences.

The direct effects of smoking on China's pulmonary health have been catastrophic. Cancers of the lung and bronchus constitute their most common malignancy across both sexes, accounting for the

Continued on following page

Continued from previous page

majority of the annual 4.3 million new cancer diagnoses (Chen et al. *CA Cancer J Clin.* 2016;66[2]:115). In Chinese men, lung cancer is the second most common cancer before the age of 60, and over the age of 75, it is the most common malignancy and also accounts for the majority of that group's cancer mortality. Women fare only slightly better, with breast cancer being their most common malignancy, but with lung cancer remaining the most pervasive across all age groups, and, by far, the most deadly (Chen, 2016). All told, of the projected 2.8 million cancer deaths occurring in 2015 in China, 21% were directly a result of lung cancer.

Likewise, COPD also threatens China. The Global Burden of Disease study conducted in 2004 demonstrated that nearly 3 million people die of COPD each year. Chinese adults over the age of 40 had an overall prevalence of COPD of 9% for the last decade, though this may be higher given the high rate of underdiagnosis in rural China (Fang X, et al. *Chest.* 2011;139[4]:920). After 2004, the Chinese Ministry of Health affirmed that COPD was the fourth leading cause of mortality in urban areas, but third in rural ones (Fang, 2011). When investigators analyzed deaths secondary to cor pulmonale coexisting with COPD, they found COPD-related mortality increased to 179.9 for men and 141.3 for women per 100,000 persons, which is about double the COPD mortality for other countries in the Asian-Pacific region (Reilly K, et al.

Am J Epidemiol. 2008;167[8]:998).

Both cancer and COPD in China disproportionately affect those in rural areas and with lower socioeconomic status, with smoking being the most potent causative exposure. On average, the annual direct and indirect per-patient cost of treating COPD amounted to about \$2,000, comprising about 40% of a family's total annual income (Fang, 2011). The cost of treating malignancy is even more expensive, but the higher likelihood of death results in an additional 10% to 20% reduction of family income when a working family member dies (Pratt, 2016). Taken together, and especially since rural Chinese citizens spend close to 20% of their income on tobacco products, the pulmonary health consequences of smoking are a significant driver of both health and economic inequality.

The Air We Breathe

Air pollution comprises a second pulmonary insult to China's health. The International Agency for Research on Cancer designated particulate matter (PM) as a class I carcinogen (Kurt O, et al. *Curr Opin Pulm Med.* 2016;22[2]:138). PM forms from combustion of bio-mass fuel, as well as from dust storms or construction. Once particulates are smaller than 2.5 microns (PM_{2.5}), they cause substantial harm to the pulmonary microenvironment. Guo and colleagues demonstrated markedly increased lung cancer risks associated with spatial mapping of ozone and PM_{2.5} concentrations (Guo Y, et al. *Environ Res.* 2016;144:60). PM_{2.5} also doubles the odds of contracting COPD in non-

smoking adults, conferring as much as a three-fold risk of contracting the disease in nonsmoking women (Fang, 2011).

Apart from causing pulmonary disease, studies also implicate air pollution as frequently causing exacerbations of existing disease. One study found an incremental increase in ED visits for respiratory illnesses for every 10 µg/m³ above the median PM_{2.5} level (Xu, et al. *PLoS One.* 2016;11(4): e0153099). In 2013, 83% of Chinese lived in places where PM_{2.5} levels exceeded China's own ambient air standard. In this cohort, elevated PM_{2.5} levels contributed directly to 300,000 premature deaths from lung cancer and COPD, with PM_{2.5} causing 1.2 million premature deaths overall (Liu J, et al. *Sci Total Environ.* 2016;568:1253).

Moving Forward

The Chinese have few illusions about these pulmonary concerns, and they are making progress. The government recently introduced stricter smoking controls in Beijing and Shanghai and continues to explore ways to decrease emissions. President Xi has put forward strong initiatives to improve the health of the Chinese. However, the nation is trying to balance its national priorities in the context of a fluid, and, at times, perilous geopolitical climate. In some ways, their position is not too dissimilar from the US geopolitical and health-care situation of the 1970s. While challenging, the issue of Chinese health care should not overshadow the remarkable resources or the truly remarkable culture of their people. Friendship, cooperation, the

reduction of suffering; these are ideals where all clinicians find common ground, regardless of nationality.

Dr. Mackay is Chief Fellow of Critical Care Medicine, Cooper University Hospital, Cooper Medical School of Rowan University, Camden, New Jersey; Dr. Flenaugh is Associate Professor of Medicine, Division Chief of Pulmonary and Critical Care Medicine, Director of Advance Diagnostic and Interventional Pulmonary, Morehouse School of Medicine, Atlanta, Georgia.

Editor's Note

This excellent, up-close Pulmonary Perspective details observations of Drs. Mackay and Flenaugh as they have participated in cross-cultural exchanges in China with realization of the many obstacles to good pulmonary health for the Chinese population, obstacles including tobacco use, COPD, and air pollution. We appreciate their bringing these observations to the forefront.

The American College of Chest Physicians, likewise concerned about pulmonary health in China, has approached the problem on a different front, working closely with partners, such as the Chinese Thoracic Society, the Chinese Association of Chest Physicians, and the Chinese Medical Doctor Association, to implement China's first ever fellowship program offering standardized training in PCCM for Chinese physicians. Read more at <http://www.mdedge.com/chestphysician/article/131179/society-news/pccm-endorsed-pilot-subspecialty-chinese-national-health>.

Nitin Puri, MD, FCCP, is the section editor of Pulmonary Perspectives.

CHEST NETWORKS

Submassive PE, antibiotic resistance, advanced practice providers

Cardiovascular Medicine and Surgery

Catch 22 of Submassive Pulmonary Emboli

Venous thromboembolism (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) occurs in approximately 1 per 1,000 patients (Piran S, Schulman S. *Thromb J.* 2016;14[S1]:23) and can be fatal. Pulmonary embolus severity is classified as low risk, intermediate-risk/submassive PE, and massive PE. There is significant controversy about the management of submassive PE, which is defined as PE with right-sided heart strain (elevated



DR. NAGEL

troponin or B-type natriuretic peptide, right-axis deviation on ECG, or evidence of RV dysfunction on CT or echocardiogram), and the absence of hypotension (systolic blood pressure > 90 mm Hg). In addition to the acute manifestations of VTE, there are potential long-term complications, including postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Several trials

have examined the utility of systemic thrombolysis in submassive PE (MAPPET-3 [Konstantinides, et al. *N Engl J Med.* 2002;347:1143], PEITHO (Meyer, et al. *N Engl J Med.* 2014;370:1402; Konstantinides, et al. *JACC.* 2017;69[12]:1536); MO-PETT (Sharifi, et al. *Am J Cardiol.* 2013;111:273); and TOPCOAT (Kline, et al. *J Thromb Haemost.* 2014;12:459), but all have failed to establish a mortality benefit. However, thrombolytics demonstrated decreased clinical deterioration and may mitigate the development of postthrombotic syndrome. Yet thrombolysis has been associated with increased bleeding (PEITHO:

11.5% vs 2.4% had major bleeding, and 2% vs 0.2% experienced hemorrhagic stroke). Current CHEST guidelines (Kearon, et al. *Chest.* 2016;149[2]:3150) recommend against the use of thrombolytics in submassive PE without hypotension. Treatment of intermediate-risk PE remains an enigma for physicians, but it is hoped that with further investigation, optimal management will be elucidated.

David J. Nagel, MD
Steering Committee Member
Olivier Axler, MD, FCCP
Vice-Chair

Continued on following page

Continued from previous page

Chest Infections

Antibiotic Resistance

One-hundred years ago, infectious diseases caused 5 of the 10 most common causes of deaths in the United States. In 2016, only one infection remained on this list (influenza/pneumonia) (*MMWR Morb Mortal Wkly Rep.* 2017;66:413).

How medicine has improved with antibiotics. An unfortunate and unintended consequence of widespread antibiotic use has been the progressive resistance to these drugs. It is estimated that, if current trends continue, 10 million



DR. FEINSTEIN

lives a year will be at risk from resistant organisms by 2050 (O'Neill, J. (2016). https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf).

Pathogens acquire antibiotic resistance by passing genetic material to one another through plasmids, bacteriophages, or naked DNA. Once acquired, resistance manifests via a number of mechanisms under the stress imposed by antibiotics (Levy SB, et al. *Nat Med.* 2004;10:S122).

Among the best studied is enzymatic degradation of the antibiotic. This occurs when beta-lactamases degrade penicillin. A second mechanism alters cell transport, thereby blocking cell entry or actively ejecting the antibiotic from the cell. Finally, overexpression or alteration of the antibiotic target may render a drug ineffective at inhibiting any vital cell function.

At the pace with which resistance now develops, the medical community faces a crisis, whereby infections caused by evolving superbugs are no longer effectively controlled by the available menu of antimicrobial agents.

This challenge must be met collectively by the more prudent prescribing of antibiotics, potentially with the help of rapid diagnostics; isolation of patients potentially infected with resistant organisms; and a focus on developing newer drugs that defy known resistant mechanisms.

Marc Feinstein, MD, FCCP
Steering Committee Member

Clinical Pulmonary Medicine

COPD and sleep-disordered breathing; A missing comorbid condition

Subjective, as well as objective, sleep complaints are common in patients with COPD (Krachman S, et al. *Proc Am Thorac Soc.* 2008;5[4]:536),

and sleeping difficulties are ranked the third most frequent complaint (behind dyspnea and fatigue) in patients with COPD (Kinsman RA, et al. *Chest.* 1983;83[5]:755). Also, sleep quality is poor, and patients with moderate to severe COPD may have higher-than-expected incidence of OSA (Soler X, et al. *Ann Am Thorac*

Soc. 2015;12[8]:1219).

Unfortunately, sleep is usually not assessed during a COPD evaluation. Up to 27% of patients with COPD without hypoxia during wakefulness can experience important desaturation during sleep, so called nocturnal oxygen desaturation (NOD) (Fletcher

Continued on following page



Avycaz[®]
ceftazidime and avibactam
for injection (2.5 g)

LEARN MORE AT AVYCAZ.COM

Please contact
your Allergan representative
for more information



© 2016 Allergan. All rights reserved.
Allergan[®] and its design are trademarks of Allergan, Inc.
AVYCAZ[®] and its design are trademarks of Forest Laboratories, LLC, an Allergan affiliate.
AVY50991 05/16

Continued from previous page

EC, et al. *Chest*. 1987;92[4]:604), that may lead to pulmonary hypertension (Chaouat A, et al. *Am J Respir Crit Care Med*. 1995;151[1]:82). Little is known about the pathophysiologic and clinical consequences



DR. SOLER

of having concomitant COPD and OSA, but recent studies have demonstrated that patients with both disorders have a high risk of hospitalizations (30-day readmission rate

for rehospitalization ranges from 20% to 39%), and death from acute exacerbations if OSA remains untreated (Marin JM, et al. *Am J Respir Crit Care Med*. 2010;182[3]:325; Machado MC, et al. *Eur Respir J*. 2010;35[1]:132). Another study has found that in patients with OSA, the presence of COPD increases the risk of death seven-fold (Lavie P, et al. *J Sleep Res*. 2007;16[1]:128).

Although identification and effective treatment of COPD comorbidities are becoming the cornerstone of COPD management, sleep-disordered breathing has not been identified in current

guidelines yet as a true potential contributor in poor outcomes despite emergent clinical evidence. Multidisciplinary programs, such as pulmonary rehabilitation, that improve dyspnea, exercise capacity, and quality of life may also positively impact sleep (Soler X, et al. *COPD*. 2013;10[2]:156). Because of the background of the staff involved, the comprehensive approach to patient assessment, and access to number of COPD subjects, pulmonary rehabilitation may be an optimal opportunity to assess sleep and identify an important comorbid condition often overlooked in patients with more advanced COPD.

Xavier Soler, MD, PhD
Steering Committee Member

Interprofessional Team

Finding Home

Outside our internal medicine curriculum, there is no formal pulmonary training or post-masters fellowship in pulmonary medicine for Advanced Practice Providers (APPs). Because of this, APPs are left to their own devices to fill educational gaps. To perform at the level expected by the physicians I work for, journal reviews and memorizing guidelines were not going to be enough. Since there is no formal pulmonary APP society, there were no peers to reach out to either.



DR. YOUNG

day with my nametag turned around worried I'd be found out as a non-physician attendee who snuck in. And then the unthinkable happened, I ran into another unicorn—another APP seeking the same information, only her nametag was turned the right way. The

Off to conferences I went.

At first, I found CHEST daunting. After all, it's run by the American College of Chest "Physicians," not Nurse Practitioners. I spent most of the first

best advice she gave was to attend the Interprofessional NetWork meeting. This was ground zero of the conference as far as I was concerned. There I found myself surrounded by RTs, RNs, NPs, PAs, and yes, even physicians.

Over the years, as I've gotten further involved with CHEST NetWorks, I have found from top to bottom CHEST striving to incorporate APPs and advance our education. From including us in the FCCP program, reducing conference pricing for APPs, and focusing this year's conference theme around being team focused, CHEST is creating a home for APPs.

Corinne Preston Young, FNP, FCCP
Steering Committee Member



CHEST®

Critical Skills for Critical Care

A State-of-the-Art Update and Procedures for ICU Providers

August 11-13

CHEST Innovation, Simulation, and Training Center



CHEST®
AMERICAN COLLEGE
OF CHEST PHYSICIANS

Join an expert panel of nurse practitioners, physician assistants, and physicians for this state-of-the-art update in critical care medicine for the whole team, featuring intensive, hands-on, and simulation-based experience in high-yield ultrasound, mechanical ventilation, and airway management procedure skills.

Attend to:

- Study the latest evidence in critical care medicine from a team-based perspective.
- Get hands-on training in ultrasound imaging and interpretation, mechanical ventilator modes and settings, and airway management for the critically ill patient.
- Participate in concise, evidence-based reviews, case-based discussions, audience response, and expert debates in areas of clinical controversy.

Target Audience

Advanced practice providers—such as nurse practitioners and physician assistants—and others practicing critical care or emergency medicine are encouraged to attend.

Learn More livelearning.chestnet.org/critical-care

CHEST®
Annual Meeting
2017

TORONTO
CANADA
October 28 - November 1



This year's focus is on the entire team, and we're busy preparing our sessions, speakers, networking events, and foundation events to make sure each experience is centered around the complete care team, so you can optimize your patient care.

The CHEST Annual Meeting offers:

- More than 400 general sessions
- Hands-on simulation sessions, virtual patient tours (VPTs), and GAMES
- Full- and half-day postgraduate tracks to accommodate all schedules
- Interdisciplinary programs designed around the entire care team, addressing clinical issues across the disciplines
- Networking and social opportunities with experts in your field

Registration Now Open

chestmeeting.chestnet.org

Learn What's New at CHEST Annual Meeting 2017

We've listened and considered all of your feedback to enhance your experience at CHEST 2017, Oct 28-Nov 1, Toronto, Canada. This year, we have changed the format of our postgraduate courses, updated our interdisciplinary sessions, and added new ways to register. Take a look at what's new.

Postgraduate courses

New this year at CHEST 2017 is the option to attend a half-day or full-day course for a more flexible experience. There are nine, half-day sessions that include lunch, and the afternoon sessions allow people to fly in that morning to

avoid an extra hotel night and missing work.

Interdisciplinary sessions

Bring your entire care team to attend programs that will address clinical issues across disciplines. Each role and perspective will be represented through session speakers, so your group can collectively experience practical, relevant updates. Sessions will combine lecture-based, case-based, and hands-on learning opportunities. Here are updated sessions:

These sessions are free but require a ticket.

Monday, October 30

- The State of PAH in 2017: An Update on the Sci-

CHEST[®] Annual Meeting 2017

ence, New Therapies, and the Changing Treatment Algorithm

- Critical Skills for ICU Directors and Their Leadership Team
- Interstitial Lung Disease: 2017 Update on Patient-Centered Management
- Lung Cancer: 2017 Update in Diagnosis and Management

Tuesday, October 31

- Challenges in ICU Management

Wednesday, November 1

- Enhancing Quality of Pulmonary Rehabilitation Programs and Integrated COPD Disease Management

Don't forget to register for CHEST 2017!

You can now register as a group! Ten or more health-care professionals from your team can register as a group for discounted tuition rates. Group registration is open through October 22 and will not be offered on-site. Learn more about CHEST 2017 updates and how to register at chestmeeting.chestnet.org.



Skyline of Toronto, Canada



2017 CHEST Education Calendar

> Learn More livelearning.chestnet.org



Live Learning Courses Courses held at the CHEST Innovation, Simulation, and Training Center in Glenview, Illinois.

Difficult Airway Management

July 14-16

Bronchoscopy and Pleural Procedures for Pulmonary and Critical Care Medicine Fellows

July 21

Mechanical Ventilation: Advanced Critical Care Management

July 28-30

Comprehensive Pleural Procedures

August 4-5

Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers

August 11-13

Ultrasonography: Essentials in Critical Care

September 15-17

December 1-3

Cardiopulmonary Exercise Testing

September 22-24

Comprehensive Bronchoscopy With Endobronchial Ultrasound

September 29 - October 1

Critical Care Ultrasound: Integration Into Clinical Practice

November 10-12

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

CHA Cambridge Health Alliance

AFFILIATED WITH
Beth Israel Deaconess Medical Center
Massachusetts General Hospital
Harvard Medical School
Tufts University School of Medicine

Pulmonary/Critical Care with Sleep Cambridge Health Alliance • Cambridge, MA

Cambridge Health Alliance (CHA) an award-winning public healthcare system, has an opportunity for a Pulmonary/ Critical Care Physician to join our existing Pulmonary team. Our system is comprised of three hospital campuses and an integrated network of both primary and specialty care practices in the Boston area. CHA is a teaching affiliate of both Harvard Medical School (HMS) and Tufts University School of Medicine.

Candidate will practice Pulmonary/CC medicine and ideally incorporate dedicated Sleep Medicine time, as well as possess a strong interest in resident and medical student teaching. Incoming physician should possess excellent clinical/communication skills and a strong commitment to serve our multicultural safety net patient population. This position has both inpatient and outpatient responsibilities. We offer a supportive and collegial environment with a strong infrastructure, inclusive of an electronic medical records system (EPIC). Candidates will have the opportunity to work in a team environment with dedicated colleagues similarly committed to providing high quality healthcare. Our employees receive competitive salary and excellent benefits.

Please send CV's to Lauren Anastasia, Department of Physician Recruitment, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge, MA 02139, via e-mail: lanastasia@challiance.org, via fax (617) 665-3553 or call (617) 665-3555. www.challiance.org. We are an equal opportunity employer and all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability status, protected veteran status, or any other characteristic protected by law.

www.challiance.org

Physician-Led Medicine in Montana

Pulmonary & Critical Care

Billings Clinic

Generous loan repayment

Join seven university-trained, board-certified Pulmonary, Critical Care and Sleep Medicine physicians. Our integrated multi-specialty physician clinic and hospital includes a Level II Trauma Center and an accredited sleep center. Practice with strong colleagues in the region's tertiary referral center.

"America's Best Town of 2016" – *Outside Magazine*

Please visit us at booth #1810 at the ATS 2017 Conference in Washington, DC!

Contact: Rochelle Woods
1-888-554-5922
physicianrecruiter@billingsclinic.org
billingsclinic.com

Billings Clinic is nationally recognized for clinical excellence and is a proud member of the **Mayo Clinic Care Network**. Located in Billings, Montana – this friendly college community is a great place to raise a family near the majestic Rocky Mountains. Exciting outdoor recreation close to home. 300 days of sunshine!

#1 Hospital in Montana
US News & World Report

CHEST
Board Review
2017

August 18 - 27 • Orlando, Florida

CRITICAL CARE SLEEP PULMONARY

Disclaimer

CHEST PHYSICIAN assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.

Moving? Look to Classified Notices for practices available in your area.

PULMONARY and CRITICAL CARE SPECIALIST

UT HEALTH NORTHEAST

UT Health Northeast is seeking a board certified or board eligible pulmonary and critical care specialist. This position has inpatient and outpatient responsibilities, and provides an opportunity for research as well as educational activities. Candidates must be eligible for licensure in Texas. We offer a competitive salary and comprehensive benefits provided by the State of Texas.

UT Health Northeast is a growing academic medical center in East Texas with approximately 75 clinical faculty in more than 25 medical specialties, as well as 32 research faculty. Graduate Medical Education is an integral component of UT Health Northeast and includes accredited residency programs in Family Medicine, Internal Medicine, and Occupational Medicine, with a Psychiatry residency planned to open in 2017. We have also recently partnered with MD Anderson to create the UT Health Northeast MD Anderson Cancer Center, which will open later this year.

For more information about this position, please contact:

Lindsay Waters
Physician Relations Representative
Lindsay.waters@uthct.edu
or by phone at 903-877-7266

FIND YOUR NEXT JOB AT

MEDJOBNETWORK.com
Physician • NP/PA Career Center

The first mobile job board for Physicians, NPs, and PAs

Mobile Job Searches—access MedJobNetwork.com on the go from your smartphone or tablet

Advanced Search Capabilities—search for jobs by specialty, job title, geographic location, employers, and more

Scan this QR code to access the mobile version of MedJobNetwork.com

CHEST Physician

CLASSIFIEDS

For Deadlines and More Information,
Contact: Drew Endy
Tel: (215) 657-2319
Email: dendy@frontlinemedcom.com

FRONTLINE
MEDICAL COMMUNICATIONS

It's been a good year for heart failure research ...

BY BRUCE JANCIN
Frontline Medical News

WASHINGTON – It's been a "relatively positive" year for heart failure research and advances in patient care, said Christopher M. O'Connor, MD, and president-elect of the Heart Failure Society of America, at the annual meeting of the American College of Cardiology.

The good news

• **Empagliflozin (Jardiance) earns FDA approval for reduction in risk of cardiovascular death in type 2 diabetes patients.** "This is one of the most amazing stories in heart failure," said Dr. O'Connor, who is also professor of medicine at Duke University in Durham, N.C.

The pivotal EMPA-REG OUT-COME study showed a highly significant 35% reduction in the secondary endpoint of risk of hospitalization for heart failure, as well the decrease in cardiovascular mortality which was the primary endpoint and proved persuasive to the FDA (N Engl J Med. 2015 Nov 26;373[22]:2117-28).

"It was a remarkable development. Because of this trial, there are now a number of ongoing phase III clinical trials looking at this class of drugs in heart failure patients with and without diabetes, which makes this a very important research movement. We are now looking deeper at phenotypes and trying to get more specific with these drug therapies," he said.

• **A new and improved LVAD is developed.** This fully magnetically levitated centrifugal-flow pump type of left ventricular assist device for advanced heart failure showed superior event-free survival, compared with a commercially available axial continuous-flow pump LVAD in the randomized MOMENTUM-3 trial (N Engl J Med. 2017 Feb 2;376[5]:440-50).

The novel pump was designed to overcome a significant problem with axial continuous-flow LVADs: a proclivity for pump thrombosis. The magnetically levitated centrifugal-flow pump proved a smashing success in this regard, with zero cases of pump thrombosis occurring during the 6-month study.

"This may be the first time in the history of heart failure research that the engineers have beaten the biologists in important clinical outcomes," the cardiologist quipped.

• **Omecamtiv mecarbil successfully addresses impaired contractility in heart failure with reduced ejection fraction (HFrEF).** This drug, a selective cardiac myosin activator, resulted



Dr. Christopher M. O'Connor

in increased duration of systole and improved stroke volume accompanied by reductions in heart rate, left ventricular end-diastolic and -systolic dimensions, and NT-proBNP in the 87-site, 13-country, phase II COSMIC-HF study (Lancet. 2016 Dec 10;388[10062]:2895-903).

"This is probably the most novel new drug mechanism out there in clinical trials," said Dr. O'Connor, who is also CEO and executive director of the Inova Heart and Vascular Institute in Falls Church, Va.

On the basis of the highly encouraging results for the surrogate endpoints assessed in COSMIC-HF, a large phase III clinical trial known as GALACTIC is underway.

• **Palliative care gets a welcome boost.** Dr. O'Connor was a coinvestigator in PAL-HF, a single-center study presented at the 2016 annual meeting of the Heart Failure Society of America.

"This is a very important trial of palliative care in advanced heart failure. We probably don't have as much evidence in this space as we should," he observed. "This was a multidisciplinary intervention in which we gave the patients a medical tool kit to alleviate pain, dyspnea, and discomfort. The tool kit included benzodiazepines, sleep medications, sublingual nitroglycerin, and morphinelike products."

The primary outcome was change in two validated heart failure quality of life measures. Both instruments documented significant improvement compared with usual care.

"There was no decrease in mortality, which wasn't a goal in this advanced heart failure population, and no reduction in heart failure hospitalizations, but there were significant reductions in depression and anxiety," Dr. O'Connor said.

• **Vericiguat is under study.** This oral soluble cyclic guanylate cyclase stimulator missed its primary endpoint in the phase II dose-escalation SOCRATES-REDUCED trial in patients with HFrEF (JAMA. 2015 Dec

1;314[21]:2251-62), but showed an impressive improvement in quality of life. It is now the subject of the ongoing, randomized, phase III VICTORIA trial involving a planned 4,000 patients with HFrEF with the composite primary endpoint of cardiovascular death or heart failure hospitalization.

The phase II SOCRATES-PRESERVED trial also missed its primary endpoint but showed a clinically meaningful improvement in quality of life in patients with heart failure with preserved ejection fraction (HFpEF) (Eur Heart J. 2017 Mar 22. doi: 10.1093/eurheartj/ehw593). Discussions are ongoing as to whether the next step should be a confirmatory phase II study or a move straight to phase III.

The bad news

• **NSAIDs linked to increased risk of heart failure.** European investigators analyzed five population-based databases totaling more than 8.3 million individuals and determined that current use of any of more than two dozen NSAIDs was associated with significantly increased risk of hospital admission for heart failure. The risk appeared to be dose dependent and varied between individual agents, ranging from a 16% increased risk with naproxen to an 83% increase with ketorolac (Toradol) (BMJ. 2016 Sep 28. doi: 10.1136/bmj.4857).

• **Therapeutic natriuretic peptides hit bottom.** The negative results for the investigational agent ularitide in patients with acute decompensated heart failure in the large phase III TRUE-AHF trial presented at the 2016 meeting of the American Heart Association, following upon an earlier negative study of the related drug nesiritide (Natrecor) in more than 7,100 acute heart failure patients (N Engl J Med. 2011 Jul 7; 365:32-43), probably spells the end of the line for this strategy of boosting outcomes in acute heart failure, according to Dr. O'Connor.

Moreover, Novartis has announced that the phase III RELAX-AHF-2 trial of serelaxin in 6,600 patients with acute heart failure failed to meet its primary endpoints of reduced cardiovascular deaths or reduced worsening of heart failure. The trial will be formally presented later this year.

"Ularitide seemed to show an early improvement in heart failure events that was not sustained in-hospital, and there was absolutely no difference in mortality. The drug probably acts like a pharmacologic tourniquet, in my view. So I think this field of therapeutic natriuretic peptides is probably closed," he said.

• **ICDs don't reduce mortality in patients with nonischemic heart failure.** This was the conclusion reached in the DANISH trial, in which more than 1,100 patients with symptomatic systolic heart failure were randomized to an ICD or usual care (N Engl J Med. 2016 Sep 29;375[13]:1221-30).

"This study really shook up the field, raising the question, 'Are we using defibrillators too frequently in this population?' It has stimulated a lot of discussion, including within the guidelines committee," Dr. O'Connor noted.

• **Tolvaptan nixed for acute decompensated heart failure.** The TACTICS-HF trial studied the use of tolvaptan (Samsca), an oral vasopressin-2 receptor antagonist, to reduce dyspnea in patients hospitalized with acute decompensated heart failure. Dr. O'Connor was a coinvestigator in the study, which showed that tolvaptan was no better than placebo at 8 and 24 hours (J Am Coll Cardiol. 2017 Mar 21;69[11]:1399-406).

"For now, the routine use of vasopressin antagonists in acute heart failure is not to be encouraged, although there may still be subsets where it's worth trying – certainly in severe hyponatremia," the cardiologist said.

• **GUIDE-IT gets lost.** This was a roughly 1,000-patient randomized trial of a treatment strategy aimed at improving clinical outcomes by aggressively titrating evidence-based heart failure therapies in order to suppress natriuretic peptide biomarkers. GUIDE-IT was stopped early by the data safety monitoring board for a lack of discernible difference in outcomes, compared with usual care.

bjancin@frontlinemedcom.com

INDEX OF ADVERTISERS

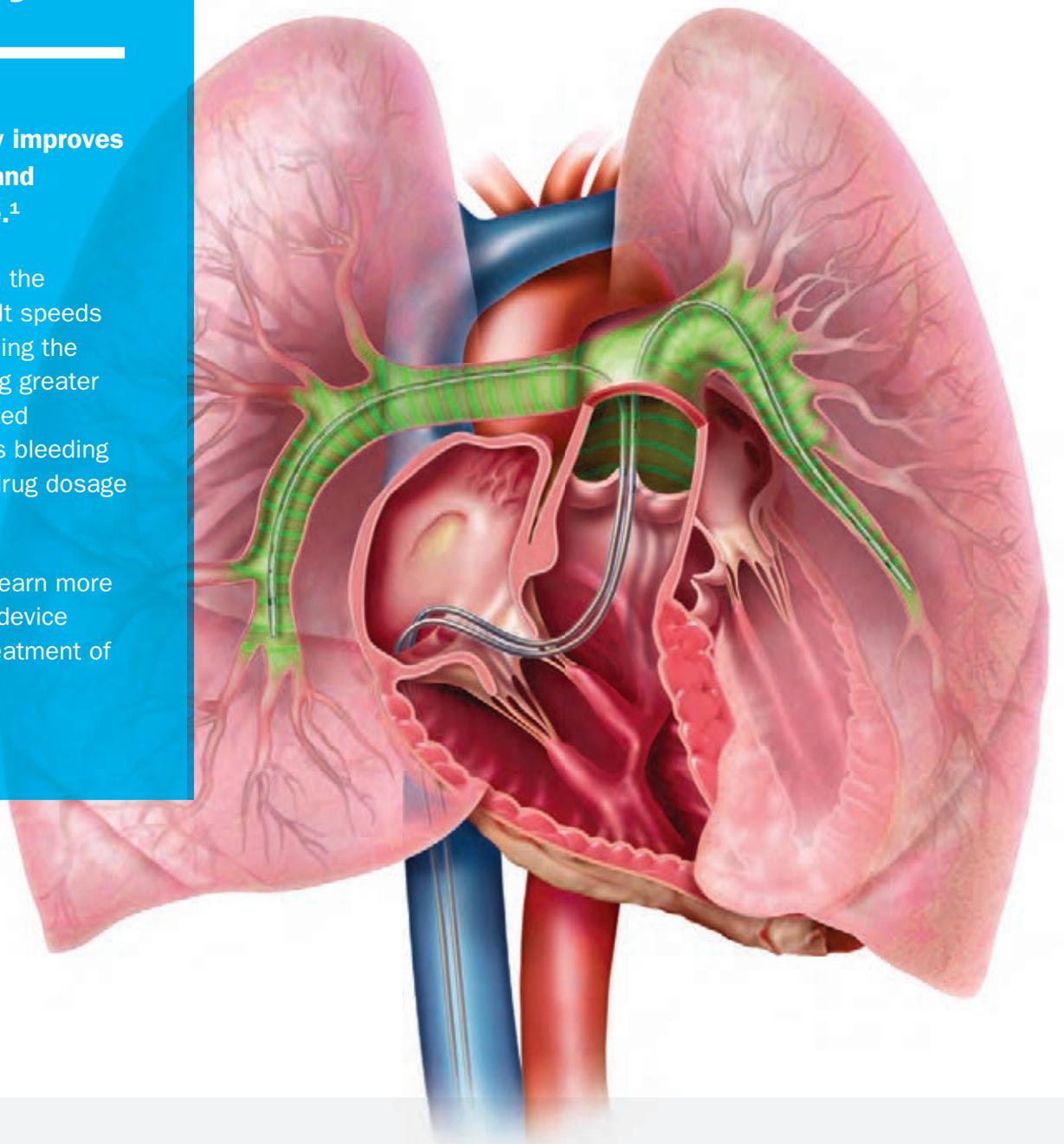
Actelion Pharmaceuticals US, Inc.	
Uptravi	8-10
Allergan	
Avycaz	39
AstraZeneca	
Symbicort	13-18
BioFire Diagnostics	
Corporate	11
Boehringer Ingelheim Pharmaceuticals, Inc.	
OFEV	25-30
Bristol-Myers Squibb	
Eliquis	20-24
EKOS Corporation	
Corporate	44
Genentech USA, Inc.	
Esbriet	2-5
United Therapeutics Corporation	
Orenitram/Remodulin/Tyvaso	32-37

Dear Clot, You really don't take my breath away.

The EKOS® System quickly improves right ventricular function and pulmonary artery pressure.¹

EKOS® does much more than the current standard of PE care. It speeds time to dissolution by unwinding the clot's fibrin structure, allowing greater lytic dispersion and accelerated absorption.² It also minimizes bleeding risk, requiring up to 4x less drug dosage than systemic delivery.^{3,4}

Visit www.ekoscorp.com to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.



¹ In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure ($P < 0.0001$) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg ($P < 0.0001$).

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.*

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. **THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS:** **Peripheral Vasculature:** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. **Pulmonary Embolism:** The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with $\geq 50\%$ clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥ 25 mmHg) or echocardiographic evaluation.

