



# CHEST<sup>®</sup> Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



COURTESY DR. APARNA SWAMINATHAN

"I suspect that genetics may play a big role in the results," said Dr. Aparna Swaminathan of Duke University.

## Poor lung function as child tied to ACOS

BY KATIE WAGNER  
LENNON  
Frontline Medical News

Children with poor lung function will be more likely to develop asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS), suggesting that prevention of this disease should be attempted in early life, a study shows.

While other research has found that patients with poor lung function in early life have poor lung function as adults, this was the first study to investigate the relationship between childhood lung function and ACOS in adult life, according to Dinh S. Bui of the University of Melbourne, and his colleagues.

The study, published in the American Journal of Respiratory and Critical Care Medicine, used multinomial regression models to investigate associations between childhood lung parameters at age 7 years and asthma, COPD, and ACOS at age 45 years (Am J Respir Crit Care Med. 2017 Feb 1. doi: 10.1164/rccm.201606-1272OC).

"We found that ACOS participants showed evidence of persistently lower FEV<sub>1</sub> [forced expiratory volume in 1 second] and FEV<sub>1</sub>/FVC [forced vital capacity] from childhood. This suggests that poorer childhood lung function tracked to early adult life, leading to impaired maximum. See **ACOS** • page 4

## Norepinephrine shortage linked to septic shock deaths

Hospitals had more deaths when deficient

BY AMY KARON  
Frontline Medical News

A national shortage of norepinephrine in the United States was associated with higher rates of mortality among patients hospitalized with septic shock, investigators reported.

Rates of in-hospital mortality in 2011 were 40% during quarters when hospitals were facing shortages and 36% when they were not, Emily Vail, MD, and her associates said at the International Symposium on Intensive Care and Emergency Medicine. The report was published simultane-

ously in JAMA.

The link between norepinephrine shortage and death from septic shock persisted even after the researchers accounted for numerous clinical and demographic factors (adjusted odds ratio, 1.2; 95% confidence interval, 1.01-1.30;  $P = .03$ ), wrote Dr. Vail of Columbia University, New York (JAMA. 2017 Mar 21. doi: 10.1001/jama.2017.2841).

Drug shortages are common in the United States, but few studies have explored their effects on patient outcomes. Investigators compared mortality. See **Septic shock** • page 7

## Pulmonary embolism common in patients with AE-COPD

BY JIM KLING  
Frontline Medical News

FROM CHEST

About 16% of patients with unexplained chronic obstructive pulmonary disease acute exacerbations (AE-COPD) had an accompanying pulmonary embolism (PE), usually in regions

that could be targeted with anticoagulants, according to a new systematic review and meta-analysis.

About 70% of the time an AE is a response to infection, but about 30% of the time, an AE has no clear cause, the authors said in a report on their research (CHEST. 2017

March;151[3]:544-54). There is a known biological link between inflammation and coagulation, which suggests that patients experiencing AE-COPD may be at increased risk of PE.

The researchers reviewed and analyzed seven studies, comprising 880 patients. See **AE-COPD** • page 8

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# HELP PRESERVE MORE LUNG FUNCTION

Reduce lung function  
decline with Esbriet<sup>1-4</sup>



## DEMONSTRATED EFFICACY\*

- Esbriet had a significant impact on lung function vs placebo in ASCEND<sup>2,3</sup>
  - 48% relative reduction in risk of a meaningful decline in lung function ( $\geq 10\%$  decline in %FVC) at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference;  $P < 0.001$ )**
  - 2.3x as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference;  $P < 0.001$ )**
- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND<sup>2,3</sup>**
- **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<sup>2,4</sup>**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)<sup>2</sup>



## ESTABLISHED MANAGEMENT PLAN

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



## COMMITTED TO PATIENTS

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



## WORLDWIDE PATIENT EXPERIENCE

- Esbriet has been approved outside the US since 2011<sup>1</sup>
- More than 27,000 patients have taken pirfenidone worldwide<sup>1</sup>

### Indication

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

### Select Important Safety Information

**Elevated liver enzymes:** Increases in ALT and AST  $> 3 \times$  ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet had a higher incidence of elevations in ALT or

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

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

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

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

Conditional recommendation, moderate confidence in estimates of effect.<sup>51</sup>

**Learn more about Esbriet and how to access medication  
at [EsbrietHCP.com](http://EsbrietHCP.com)**

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

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

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

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

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

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

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

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

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

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

**You may report side effects to the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). You may also report side effects to Genentech at 1-888-835-2555.**

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

**References:** **1.** Data on file. Genentech, Inc. 2015. **2.** Esbriet Prescribing Information. Genentech, Inc. September 2015. **3.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med*. 2014;371(12):1172]. *N Engl J Med*. 2014;370(22):2083-2092. **4.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet*. 2011;377(9779):1760-1769. **5.** Raghu G, Rochweg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline [published correction appears in *Am J Respir Crit Care Med*. 2015;192(5):644]. *Am J Respir Crit Care Med*. 2015;192(2):e3-e19.

**Esbriet**<sup>®</sup>  
(pirfenidone) capsules 267mg

# Low FEV<sub>1</sub> nearly triples ACOS risk

ACOS from page 1

imally attained lung function,” the researchers said.

“The study highlights that low childhood lung function is a risk factor for COPD (and ACOS) indepen-

dent of smoking,” they noted.

The 1,355 study participants who had postbronchodilator (post-BD) lung function available were categorized into the following four mutually

exclusive groups at age 45 years based on their asthma and COPD status: having neither asthma nor COPD (unaffected) (n = 959); having asthma alone (n = 269); having COPD alone (n = 59); having ACOS (n = 68).

Once adjusted for the sampling weights, the prevalence of current asthma alone was 13.5%, COPD alone

was 4.1%, and ACOS was 2.9%. The researchers defined COPD at age 45 years as post-BD FEV<sub>1</sub>/FVC less than the Global Lung Initiative lower limit of normal. Because the associations between childhood lung function and both ACOS and COPD alone were nonlinear, the patients were grouped into quartiles based on their character-

**Esbriet**  
(pirfenidone) capsules 267mg

Rx only

## BRIEF SUMMARY

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

## 1 INDICATIONS AND USAGE

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

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Elevated Liver Enzymes

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

### 5.2 Photosensitivity Reaction or Rash

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

### 5.3 Gastrointestinal Disorders

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

## 6 ADVERSE REACTIONS

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

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

## ESBRIET® (pirfenidone)

### 6.1 Clinical Trials Experience

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

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

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

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

The most common adverse reactions with an incidence of  $\geq 10\%$  and more frequent in the ESBRIET than placebo treatment group are listed in Table 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 <sup>1</sup>	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%

<sup>1</sup> Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

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

### 6.2 Postmarketing Experience

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

*Blood and Lymphatic System Disorders*  
Agranulocytosis

*Immune System Disorders*  
Angioedema

*Hepatobiliary Disorders*

Bilirubin increased in combination with increases of ALT and AST

istics, such as their percent predicted FEV<sub>1</sub> and percent predicted FEV<sub>1</sub>/FVC at 7 years, the investigators said.

Patients in the lowest quartile for FEV<sub>1</sub> percent predicted at 7 years were 2.93 times more likely to have ACOS, compared with patients in the other quartiles for FEV<sub>1</sub> percent predicted. Patients in the lowest quartile

for FEV<sub>1</sub>/FVC percent predicted at 7 years were 16.3 times more likely to have ACOS and 5.76 times more likely to have COPD alone, compared with patients in the higher quartiles.

The researchers found large variation in childhood lung function among patients in the lowest quartiles for FEV<sub>1</sub> and FEV<sub>1</sub>/FVC. To account

for this, they conducted a sensitivity analysis, which excluded those with less than 80% predicted FEV<sub>1</sub> and FEV<sub>1</sub>/FVC (n = 76 and 13, respectively). The associations between lung function measures and diseases in adulthood for patients in the lowest quartiles differed slightly following this adjustment. The sensitivity analy-

sis showed that patients in the lowest quartile for FEV<sub>1</sub> had an odds ratio of 2.4 for ACOS and that those patients in the lowest quartile for FEV<sub>1</sub>/FVC had an odds ratio of 5.2 for COPD alone and 15.1 for ACOS.

A sensitivity analysis that excluded patients with remitted asthma from the unaffected group showed childhood FEV<sub>1</sub> was more strongly associated with ACOS for patients in the lowest quartile, compared with patients in the highest quartile (OR, 7.0; 95% confidence interval, 2.7-18.3). This same analysis found that patients from the lowest quartile and second quartile for childhood FEV<sub>1</sub>/FVC were 6.8 and 3.9 times more likely to have COPD, respectively, compared with patients in the other quartiles. This sensitivity analysis also found that patients in the first quartile for FEV<sub>1</sub>/FVC were 19.1 times more likely to have ACOS, and patients in the second quartile for FEV<sub>1</sub>/FVC were 5.3 times more likely to have ACOS.

The researchers analyzed data from the Tasmanian Longitudinal Health Study, which began in 1968 when Tasmanian children born in 1961 and attending school in Tasmania were studied with respiratory health surveys and prebronchodilator (pre-BD) spirometry measurements. The most recent survey started in 2002. Survey respondents who had participated in past follow-up studies and/or reported symptoms of asthma or cough were invited to participate in a more detailed laboratory study from 2006 to 2008. That study included completing a questionnaire, pre-BD and post-BD spirometry, and skin prick testing. The predicted and percent predicted values for spirometry were derived from the Global Lung Initiative reference equations.

The final multinomial model was adjusted for childhood asthma, maternal smoking, paternal smoking during childhood, and other factors.

History of active smoking was significantly more frequent in patients with ACOS (73.5%) and COPD alone (73%) than in the unaffected (57%) groups. Childhood asthma, maternal asthma, and atopy were more prevalent in the ACOS and asthma alone groups. ACOS and COPD participants had a higher prevalence of maternal smoking during childhood.

Individuals with ACOS had the lowest pre-BD FEV<sub>1</sub> (percent predicted values) over time. Those with COPD alone or ACOS had significantly lower pre-BD FEV<sub>1</sub>/FVC (percent predicted values) at all time points, when patients were assessed, compared with unaffected participants. "Participants with COPD alone had significantly higher

*Continued on following page*

## ESBRIET® (pirfenidone)

### 7 DRUG INTERACTIONS

#### 7.1 CYP1A2 Inhibitors

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

#### Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see *Clinical Pharmacology section 12.3 in full Prescribing Information*]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.4 in full Prescribing Information*].

#### Moderate CYP1A2 Inhibitors

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

#### Concomitant CYP1A2 and other CYP Inhibitors

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

#### 7.2 CYP1A2 Inducers

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m<sup>2</sup> basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m<sup>2</sup> basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m<sup>2</sup> basis at a maternal dose of 1000 mg/kg/day).

#### 8.3 Nursing Mothers

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

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

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

## ESBRIET® (pirfenidone)

### 8.6 Hepatic Impairment

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

### 8.8 Smokers

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

### 10 OVERDOSAGE

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

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

### 17 PATIENT COUNSELING INFORMATION

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

#### Liver Enzyme Elevations

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

#### Photosensitivity Reaction or Rash

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

#### Gastrointestinal Events

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

#### Smokers

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

#### Take with Food

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

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Continued from previous page

FVC at 7 and 13 years, while ACOS participants had significantly lower FVC at 45 years,” the researchers said.

“There was no evidence of effect modification by childhood lung infections, childhood asthma, maternal asthma, maternal smoking, or paternal smoking during childhood on the associations between childhood lung function and the disease groups,” they noted.

The study was limited by its “relatively small sample sizes for the ACOS and COPD alone groups” and the absence of post-BD spirometry at 7 years, they added.

The researchers concluded that “screening of lung function in school-aged children may provide an opportunity to detect children likely to have ongoing poorer lung health, such as those with lung function below the lower limit of normal,”

and that “[multifaceted] intervention strategies could then be implemented to reduce the burden of COPD and ACOS in adulthood.”

Asked to comment on the study, Aparna Swaminathan, MD, a pulmonary/critical care fellow at Duke University, Durham, N.C., and a Duke Clinical Research Institute fellow, said she would want to know “what is driving the effects in the study” before designing an intervention.

“I suspect that genetics may play a big role in the results, and there is increasing interest in learning how genetics are involved in COPD. A better understanding of the risk factors for lower lung function in children may also provide targets of intervention. The groups with ACOS and COPD have higher rates of maternal smoking, and while this study determined that the association between childhood low lung function and development of COPD and ACOS is independent of

maternal smoking, maternal smoking still seems like a good area to target,” she said in an interview.

It would also be interesting to further study the first quartile of patients, she added. “The clinical



**A population of children with low lung function today may be experiencing relatively less asthma.**

DR. GARTMAN

disease for this quartile of patients covers a wide range of severities. I would be interested in dividing this group up further and learning the outcomes of their lung function and development of COPD and ACOS.”

Aggressively treating childhood asthma and poor lung function is one method that may have altered the destiny of the children with lower lung function, if it had been used, said Eric Gartman, MD, FCCP, in an interview.

Using inhaled corticosteroids and other medications for maintenance control, reducing and monitoring impairment, educating patients and patients’ guardians on triggers, avoiding triggers, and having an action plan for changing therapy based on symptoms or measured flows are ways to aggressively treat such conditions, said Dr. Gartman, assistant professor of medicine at Brown University, Providence, R.I. He cited avoiding exposure to smoke, environmental pol-

lutants, and living near highways, for those with low childhood function, as interventions that might prevent people with low lung function from later developing COPD.

Dr. Gartman added that differences between the availability of medication for children with asthma today and at the time of the study may mean there are differences between the children with low lung function in the study and those children who have low function today. A population of children with low lung function now may be experiencing relatively less asthma and more chronic lung disorders brought on by prematurity or cystic fibrosis, he noted. “As such, identification of poor function in today’s young children may carry with it a significantly different set of interventions and challenges,” Dr. Gartman said.

While asthma in children is better controlled now than it was at the time of the study, because the researchers did not provide any information about the asthma control of the study participants, “it [is] hard for me to say if better asthma drugs in those children would have made a difference in long-term outcomes of COPD and ACOS as an adult,” Dr. Swaminathan noted.

“The best thing we currently can do for children with low lung function is try and determine the underlying cause and treat any active diseases [such as asthma] that we can. This study reminds us of the need to keep searching for causes of low lung function that may be reversible,” she said.

The investigators recommended future research to understand the

Continued on following page

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

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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.

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# STEMI team repurposed for rapid treatment of PEs

BY TED BOSWORTH  
Frontline Medical News

WASHINGTON – The in-hospital team responsible for rapid management of ST-elevation myocardial infarction (STEMI) may also be the right team to manage pulmonary embolism (PE), according to a pilot study associating this approach with rapid treatment times and low overall mortality rates.

The data from the pilot study suggest that arming the STEMI team with a protocol for managing PE “is an effective means to care for patients with massive and submassive pulmonary embolism,” said Michael R. Kendall, MD, of the University of Southern California, Los Angeles. He presented the findings at the 2017 Cardiovascular Research Technologies meeting.

There are obvious parallels between STEMI and PE. Like STEMI, PE requires rapid diagnosis, triage, and when appropriate, an endovascular procedure. This led the USC investigators to consider a formal pilot study to test the premise that the STEMI team is in a position to deliver urgent care and good outcomes to PE patients.

The objective of the pilot study was “to evaluate treatment times and clinical outcome for patients with massive and submassive PE using a dedicated PE protocol,” Dr. Kendall explained. Massive PE was defined as hemodynamic instability with systolic blood pressure below 90 mm Hg or requiring inotropic support. Submassive PE was defined as systolic BP greater than 90 mm Hg with right heart dysfunction, such as a dilated right ventricle and elevated troponin levels.

**Even though treatment approaches were not standardized, the protocol for diagnosing and managing PE on an urgent basis produced encouraging times for delivery of care and outcomes, Dr. Kendall noted.**

Over an 18-month period beginning in June 2014, 40 PE patients were treated. The average age was 55 years, 50% were obese, 32% had renal insufficiency, 30% had recent surgery or had recently been immobilized, 30% had a history of deep venous thrombosis, and 28% had an active malignancy. At 43%, the largest single source of cases was the emergency department (ED), while 38% were transferred in from other centers, and 19% were already hospitalized at the time of the PE.

All patients underwent computed tomographic pulmonary angiography (CTPA) as part of the diagnostic procedure prior to an invasive angiogram. Patients received one or more different treatments upon confirmation of the PE, including catheter-directed thrombolytics, rheolytic thrombectomy, mechanical fragmentation, mechanical aspiration, and surgical pulmonary embolectomy. Inferior vena cava filters were used as appropriate.

At presentation, 10% were in cardiac arrest, 22% required intubation, and 12% required extracorporeal membrane oxygenation. On the basis of the diagnostic studies, 57% had a massive PE, and the remainder had submassive disease.

The average time from door to CTPA among those presenting to the ED was roughly 5 hours. It took, on average, an additional 2 hours from CTPA to an invasive angiogram, and another 3 hours to treatment, producing a total average door to treatment time of 10 hours.

Most patients received rheolytic thrombectomy, often with another form of treatment, such as catheter-directed thrombolytics, but 15% were

treated with anticoagulation alone. Although a few patients improved sufficiently to obviate the need for an invasive procedure, the remainder of the patients received anticoagulation alone because of contraindications for invasive strategies or treatment refusal.

The average length of a hospital stay was 15 days. Bleeding events occurred in 10% of patients and 18% required a blood transfusion. Survival to hospital discharge was 82%. Although there was no control group, this rate of survival was considered favorable in the context of the severity of the PE.

Overall, delivery of urgent care for PE by a STEMI team was found feasible. Even though treatment approaches were not standardized, the protocol for diagnosing and managing PE on an urgent basis produced encouraging times for delivery of care and outcomes, according to the data presented by Dr. Kendall. Because of the differences in the composition and function of the STEMI team, Dr. Kendall indicated that it is difficult to predict similar success at other centers, but the findings overall were considered positive.

The senior author of the study, David M. Shavelle, MD, also at USC, suggested that the program there might be a template. He believes that the STEMI team has the skills to deliver prompt PE care, and he believes that this approach would be appropriate at other centers. He also suggested that such formal programs may be useful in establishing better treatment protocols.

“For PE, there are no clear guidelines for treatment time intervals, such as time from door to endovascular treatment,” Dr. Shavelle observed. He said that the wide variation of devices currently being used for treatment complicates efforts to develop clear clinical protocols and measure outcomes, and he “would like to see more standardization of treatment and registries to address these areas.”

Dr. Kendall reported no financial relationships.

*Continued from previous page*

risk factors for lower lung function in children. They called for studies that address “the risk factors over adulthood that interact with lower lung function to increase the risk of rapid lung function decline.”

The study was supported by a National Health and Medical Research Council of Australia research grant; the University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland, & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; GlaxoSmithKline; and John L Hopper. Five authors were supported by the research grant; the others reported no conflicts. Dr. Swaminathan and Dr. Gartman had no disclosures.

klennon@frontlinemedcom.com

## At nadir, 56% got top vasopressor

Septic shock from page 1

rates among affected patients during 3-month intervals when hospitals were and were not using at least 20% less norepinephrine than baseline. The researchers used Premier Healthcare Database, which includes both standard claims and detailed, dated logs of all services billed to patients or insurance, with minimal missing data.

A total of 77% patients admitted with septic shock received norepinephrine before the shortage. During the lowest point of the shortage, 56% of patients received it, the researchers reported. Clinicians most often used phenylephrine instead, prescribing it to up to 54% of patients during the worst time of the shortage. The absolute increase in mortality during the quarters of shortage was 3.7% (95% CI, 1.5%-6.0%).

Several factors might explain the link between norepinephrine shortage and mortality, said the investigators. The vasopressors chosen to replace norepinephrine might result directly in worse outcomes, but a decrease in norepinephrine use also might be a proxy for relevant variables such as delayed use of vasopressors, lack of knowledge of how to optimally dose vasopressors besides norepinephrine, or the absence of a pharmacist dedicated to helping optimize the use of limited supplies.

The study did not uncover a dose-response association between greater decreases in norepinephrine use and increased mortality, the researchers noted. “This may be due to a threshold effect of vasopressor shortage on mortality, or

lack of power due to relatively few hospital quarters at the extreme levels of vasopressor shortage,” they wrote.

Because the deaths captured included only those that occurred in-hospital, “the results may have underestimated mortality, particularly for hospitals that tend to transfer patients early to other skilled care facilities,” the researchers noted.

The cohort of patients was limited to those who received vasopressors for 2 or more days and excluded patients who died on the first day of vasopressor treatment, the researchers said.

The Herbert and Florence Irving Scholars Program at Columbia University provided funding.

One coinvestigator disclosed grant funding from the National Institutes of Health and personal fees from UpToDate. The other investigators reported having no conflicts of interest.

# CF patients live longer in Canada than in U.S.

BY MARY ANN MOON  
Frontline Medical News

People with cystic fibrosis (CF) survive an average of 10 years longer if they live in Canada than if they live in the United States, according to a report published online March 14 in *Annals of Internal Medicine*.

Differences between the two nations' health care systems, including access to insurance, "may, in part, explain the Canadian survival advantage," said Anne L. Stephenson, MD, PhD, of St. Michael's Hospital, Toronto, and her associates.

Previous studies have suggested a significant survival gap between Americans and Canadians with CF, but their conclusions were "problematic" because of inherent differences between the two countries in registry data, which complicated direct comparisons. Dr. Stephenson and her associates used several statistical strategies to adjust for these differences, and confirmed the discrepancy in survival by analyzing information for 45,448 U.S. patients and 5,941 Canadian patients treated at 110 U.S. and 42 Canadian specialty centers from 1990 through 2013.

Overall there were 9,654 U.S. deaths and 1,288 Canadian deaths during the study period, for

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** This study highlights that more investigations need to be done comparing the two systems. Is the



life expectancy related to insurance issues, compliance with follow-up visits, colonization with resistant organisms, or frequency of transplantation, for example? These questions need to be answered quickly to help advocate for the health of cystic fibrosis patients!

nearly identical overall mortality between the two countries (21.2% and 21.7%, respectively). However, the median survival was 10 years longer in Canada (50.9 years) than in the United States (40.6 years), a gap that persisted across numerous analyses that adjusted for patient characteristics and clinical factors, including CF severity.

One particular difference between the two study populations was found to be key: Canada has single-payer universal health insurance, while the United States does not. When U.S. patients were

categorized according to their insurance status, Canadians had a 44% lower risk of death than did U.S. patients receiving continuous Medicaid or Medicare (95% confidence interval, 0.45-0.71;  $P$  less than .001), a 36% lower risk than for U.S. patients receiving intermittent Medicaid or Medicare (95% CI, 0.51-0.80;  $P$  = .002), and a 77% lower risk of death than U.S. patients with no or unknown health insurance (95% CI, 0.14-0.37;  $P$  less than .001), the investigators said (*Ann. Intern. Med.* 2017 Mar 14. doi: 10.7326/M16-0858).

In contrast, there was no survival advantage for Canadian patients when compared with U.S. patients who had private health insurance. This "[raises] the question of whether a disparity exists in access to therapeutic approaches or health care delivery," the researchers noted.

This study was supported by the U.S. Cystic Fibrosis Foundation, Cystic Fibrosis Canada, the National Institutes of Health, and the U.S. Food and Drug Administration. Dr. Stephenson reported grants from the Cystic Fibrosis Foundation and fees from Cystic Fibrosis Canada. Several of the study's other authors reported receiving fees from various sources and one of those authors reported serving on the boards of pharmaceutical companies.

## Five studies identified PE location

AE-COPD from page 1

Among the authors' reasons for conducting this research was to update the pooled prevalence of PE in AE-COPD from a previous systematic review published in *CHEST* in 2009.

The meta-analysis revealed that 16.1% of patients with AE-COPD were also diagnosed with PE (95%

confidence interval, 8.3%-25.8%). There was a wide range of variation between individual studies (prevalence, 3.3%-29.1%). In six studies that reported on deep vein thrombosis, the pooled prevalence of DVT was 10.5% (95% CI, 4.3%-19.0%).

Five of the studies identified the PE location. An analysis of those studies showed that 35.0% were in the main pulmonary artery, and 31.7% were in the lobar and inter-lobar arteries. Such findings suggest that "the majority of these embolisms have important clinical consequences," the authors wrote.

The researchers also looked at clinical markers that accompanied AE-COPD and found a potential signal with respect to pleuritic chest pain. One study found a strong association between pleuritic chest pain and AE-COPD patients with PE (81.0% versus 40.0% in those without PE). A second study showed a similar association (24.0% in PE versus 11.5% in non-PE patients), and a third study found no significant difference.

The presence of PE was also linked to hypotension, syncope, and acute right failure on ultrasonography, suggesting that PE may be associated with heart failure.

## VIEW ON THE NEWS

**Vera A. De Palo, MD, MBA, FCCP, comments:** Many of us have been trained with the clinical pearl, "If you think PE, treat PE." This work helps to illuminate another clinical scenario, the acute exacerbation



of COPD, where PE may play a role in the clinical course and outcome. The authors advise to think of PE in those acute exacerbation COPD patients with pleuritic chest pain and signs of heart failure. Clinical suspicion should play a role in determining the diagnostic testing. This knowledge may not only help us to recognize more cases where pulmonary embolism may play a role, but may help us provide treatment earlier and may reduce mortality from this serious clinical disease.

Patients with PE were less likely to have symptoms consistent with a respiratory tract infection. They also

**Thirty-five percent of the PEs were in the main pulmonary artery, and 31.7% were in the lobar and inter-lobar arteries, suggesting that "the majority of these embolisms have important clinical consequences," the authors noted.**

tended to have higher mortality rates and longer hospitalization rates compared with those without PE.

The meta-analysis had some limitations, including the heterogeneity of findings in the included studies, as

well as the potential for publication bias, since reports showing unusually low or high rates may be more likely to be published, the researchers noted. There was also a high proportion of male subjects in the included studies.

Overall, the researchers concluded that PE is more likely in patients with pleuritic chest pain and signs of heart failure, and less likely in patients with signs of a respiratory infection. That information "might add to the clinical decision-making in patients with an AE-COPD, because it would be undesirable to perform [computed tomography pulmonary angiography] in every patient with an AE-COPD," the researchers wrote.

The study received no funding. The authors reported having no financial disclosures.

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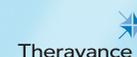


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BREO is for adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA.

BREO is NOT indicated for the relief of acute bronchospasm.

### Important Safety Information

#### WARNING: ASTHMA-RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

BOXED WARNING CONTINUED ON NEXT PAGE

Please see additional Important Safety Information for BREO on pages 2–4.

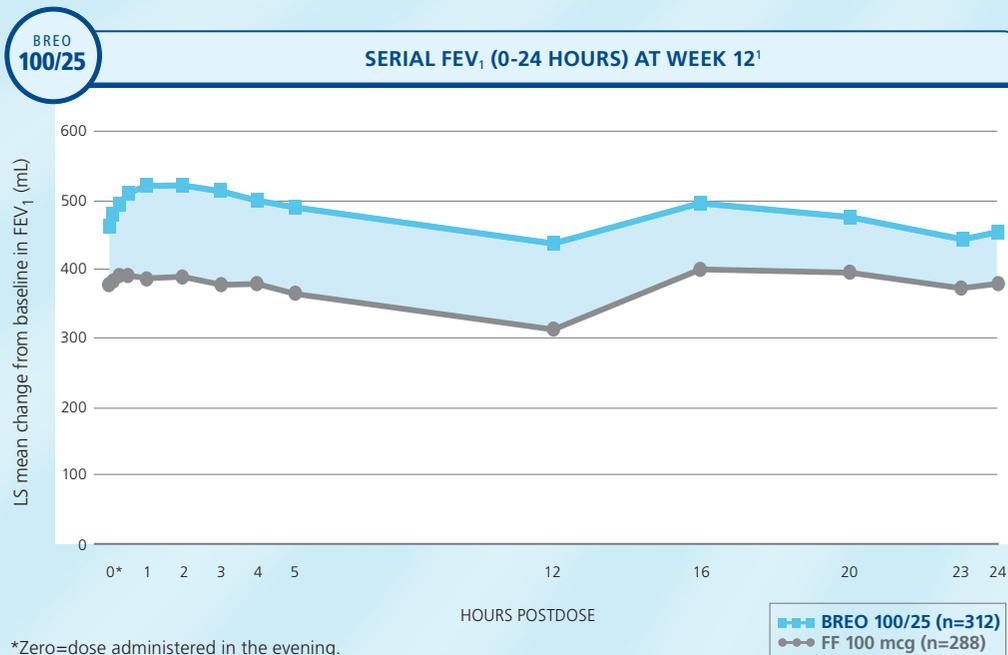
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.



# BREO: CONTINUOUS LUNG FUNCTION IMPROVEMENT

## In patients with asthma uncontrolled on an ICS

BREO 100/25 (n=312) provided a 108-mL improvement from baseline in weighted mean (wm) FEV<sub>1</sub> (0-24 hours) vs fluticasone furoate (FF) 100 mcg (n=288) at Week 12 ( $P<0.001$ ).<sup>1</sup>



### Study description

**Design:** 12-week, randomized, double-blind study that evaluated the safety and efficacy of BREO 100/25, BREO 200/25, and FF 100 mcg (each administered once daily in the evening). Patients who reported symptoms and/or rescue beta<sub>2</sub>-agonist use during a 4-week run-in period on mid- to high-dose ICS ( $\geq 250$  mcg fluticasone propionate [FP] twice daily or equivalent) were randomized to treatment.

**Patients:** 1039 patients with asthma aged 12 years and older<sup>††</sup> (mean age: 46 years). At baseline, patients had a mean percent predicted FEV<sub>1</sub> of 62%.

<sup>††</sup> BREO is approved for use in patients  $\geq 18$  years of age.

**Primary endpoint:** wm FEV<sub>1</sub> (0-24 hours) at Week 12.

Weighted mean FEV<sub>1</sub> (0-24 hours) was calculated from predose FEV<sub>1</sub> (within 30 minutes of dose) and postdose FEV<sub>1</sub> after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours.

FEV<sub>1</sub>=forced expiratory volume in 1 second; LS=least squares.

### In a placebo-controlled 12-week study<sup>2</sup>:

- **wm FEV<sub>1</sub>:** in a subset of patients, BREO 100/25 (n=108) demonstrated a numerically greater improvement in change from baseline in wm FEV<sub>1</sub> (0-24 hours) compared with FF 100 mcg (n=106) of 116 mL (95% CI: -5, 236;  $P=0.06$ ) and a statistically significant 302-mL improvement ( $P<0.001$ ) compared with placebo (n=95) at Week 12.

**Study description:** 12-week, randomized, double-blind, placebo-controlled study of 609 patients aged 12 years and older<sup>†</sup> (mean age: 40 years) with asthma, symptomatic on low- to mid-dose ICS (FP 100 mcg to 250 mcg twice daily or equivalent) during a 4-week run-in period (mean baseline percent predicted FEV<sub>1</sub> of 70%) randomized to BREO 100/25, FF 100 mcg, or placebo (each administered once daily in the evening). The co-primary endpoints were weighted mean FEV<sub>1</sub> (0-24 hours) (in a subset of patients) and trough FEV<sub>1</sub> at Week 12.

<sup>†</sup>BREO is approved for use in patients  $\geq 18$  years of age.

## Important Safety Information (cont'd)

### WARNING: ASTHMA-RELATED DEATH (BOXED WARNING cont'd)

**When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.**

## CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

## WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

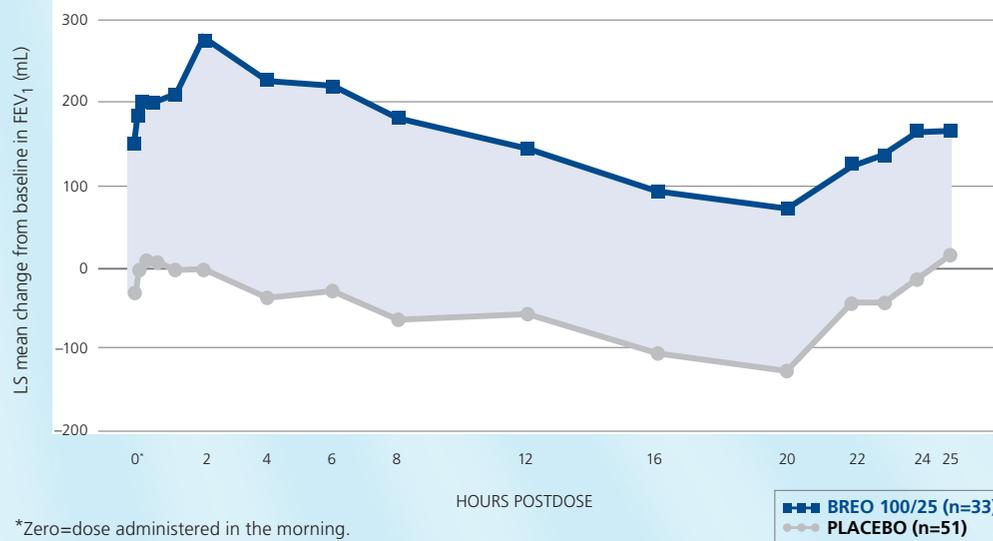
# FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

## In patients with COPD

BREO 100/25 (n=33) provided a 220-mL improvement from baseline in wm FEV<sub>1</sub> (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (P<0.001).<sup>3,4</sup>

BREO  
100/25

SERIAL FEV<sub>1</sub> (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29<sup>3,4</sup>



\*Zero=dose administered in the morning.

### Study description

**Design:** randomized, double-blind, crossover study compared the effect of 28 days of treatment with BREO 100/25 and placebo (each administered once daily in the morning) on lung function over 24 hours.

**Patients:** 54 patients (mean age: 58 years) with COPD who had a mean percent predicted postbronchodilator FEV<sub>1</sub> of 50% and a mean postbronchodilator FEV<sub>1</sub>/FVC ratio of 53%.

**Primary endpoint:** wm FEV<sub>1</sub> (0-24 hours) at end of 28-day treatment period.

**Secondary endpoint:** serial FEV<sub>1</sub> (0-25 hours) assessed over 1 full day at Days 28 and 29.

FVC=forced vital capacity.

BREO 100/25 is the only strength indicated for COPD.

**In a separate 6-month lung-function study:** a randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs FF 100 mcg and vs placebo (each administered once daily) on lung function in 1030 patients (mean age: 63 years) with COPD.<sup>5</sup> For the co-primary endpoints, BREO significantly improved wm FEV<sub>1</sub> (0-4 hours) postdose on Day 168 by 120 mL vs FF<sup>II</sup> and 173 mL vs placebo (P<0.001 for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV<sub>1</sub> at Day 169 of 115 mL vs placebo (95% CI: 60, 169; P<0.001); the 48-mL difference vs vilanterol (VI) 25 mcg<sup>†</sup> did not achieve statistical significance (95% CI: -6, 102; P=0.082).<sup>3,5</sup>

<sup>5</sup>At screening, patients had a mean postbronchodilator percent predicted FEV<sub>1</sub> of 48% and a mean postbronchodilator FEV<sub>1</sub>/FVC ratio of 48%.

<sup>II</sup>The wm comparison of BREO with FF, the ICS component, evaluated the contribution of VI to BREO. ICS are not approved as monotherapy for COPD.

<sup>†</sup>The trough FEV<sub>1</sub> comparison of BREO with VI, the LABA component, evaluated the contribution of FF to BREO. VI is not approved as monotherapy.

## Important Safety Information (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal.
  - In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/vilanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (<1% for each treatment group).

**References:** 1. Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma*. 2015;52(10):1073-1083. 2. Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561. 3. Data on file, GSK. 4. Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012;34(8):1655-1666. 5. Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomized trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. *Respir Med*. 2013;107(4):560-569.

Please see additional Important Safety Information for BREO on pages 1, 2, and 4.

Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5-7.

**BREO<sup>®</sup> ELLIPTA<sup>®</sup>**  
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

# CONSIDER 24-HOUR BREO TODAY

## Important Safety Information (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

### ADVERSE REACTIONS: BREO 100/25 FOR COPD

- The most common adverse reactions ( $\geq 3\%$  and more common than placebo) reported in two 6-month clinical trials with BREO (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).
- In addition to the events reported in the 6-month studies, adverse reactions occurring in  $\geq 3\%$  of the subjects with COPD treated with BREO in two 1-year studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

### ADVERSE REACTIONS: BREO FOR ASTHMA

- In a 12-week trial, adverse reactions ( $\geq 2\%$  incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis, 10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions ( $\geq 2\%$  incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% ( $<1\%$ ); and cough, 1% (2%).
- In addition to the adverse reactions reported in the two 12-week trials, adverse reactions ( $\geq 2\%$  incidence) reported in subjects taking BREO 200/25 once daily in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia, and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
- In a 24- to 76-week trial of subjects with a history of 1 or more asthma exacerbations within the previous 12 months, asthma-related hospitalizations occurred in 1% of subjects treated with BREO 100/25. There were no asthma-related deaths or asthma-related intubations observed in this trial.

### DRUG INTERACTIONS

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

### USE IN SPECIFIC POPULATIONS

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

**Please see additional Important Safety Information for BREO on pages 1–3. Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.**

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BREO ELLIPTA was developed in collaboration with Theravance

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**BREO<sup>®</sup> ELLIPTA<sup>®</sup>**  
(fluticasone furoate 100 mcg and  
vilanterol 25 mcg inhalation powder)

## BRIEF SUMMARY

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

The following is a brief summary only; see full prescribing information for complete product information.

### WARNING: ASTHMA-RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS [see Warnings and Precautions (5.1)].

## 1 INDICATIONS AND USAGE

### 1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease:

BREO 100/25 is a combination inhaled corticosteroid/long-acting beta<sub>2</sub>-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.

**Important Limitation of Use:** BREO is NOT indicated for the relief of acute bronchospasm.

### 1.2 Treatment of Asthma:

BREO is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older. LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.4)]. Therefore, when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

**Important Limitation of Use:** BREO is NOT indicated for the relief of acute bronchospasm.

## 4 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Asthma-Related Death:

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore,

when treating patients with asthma, physicians should only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

### 5.2 Deterioration of Disease and Acute Episodes:

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

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta<sub>2</sub>-agonist becomes less effective; or the patient needs more short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.

When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta<sub>2</sub>-agonist and instruct the patient on how it should be used.

### 5.3 Excessive Use of BREO and Use with Other Long-Acting Beta<sub>2</sub>-Agonists:

BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

### 5.4 Local Effects of ICS:

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

### 5.5 Pneumonia:

An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO 100/25 in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 6% (51 of 806 subjects); or BREO 200/25: 7% (55 of 811 subjects) than in subjects receiving vilanterol 25 mcg: 3% (27 of 818 subjects). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal

pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (less than 1% for each treatment group).

### 5.6 Immunosuppression:

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

### 5.7 Transferring Patients from Systemic Corticosteroid Therapy:

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

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV<sub>1</sub> or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

### 5.8 Hypercorticism and Adrenal Suppression:

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].

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

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

### 5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:

Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,

troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [see *Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information*].

#### 5.10 Paradoxical Bronchospasm:

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

#### 5.11 Hypersensitivity Reactions, Including Anaphylaxis:

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

#### 5.12 Cardiovascular Effects:

Vilanterol, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

#### 5.13 Reduction in Bone Mineral Density:

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

#### 5.14 Glaucoma and Cataracts:

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

#### 5.15 Coexisting Conditions:

BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

#### 5.16 Hypokalemia and Hyperglycemia:

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

#### 5.17 Effect on Growth:

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

### 6 ADVERSE REACTIONS

**LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent**

**patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. [See Warnings and Precautions (5.1).]**

Systemic and local corticosteroid use may result in the following: *Candida albicans* infection [see *Warnings and Precautions (5.4)*]; Increased risk of pneumonia in COPD [see *Warnings and Precautions (5.5)*]; Immunosuppression [see *Warnings and Precautions (5.6)*]; Hypercorticism and adrenal suppression [see *Warnings and Precautions (5.8)*]; Reduction in bone mineral density [see *Warnings and Precautions (5.13)*]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

#### 6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:

The clinical program for BREO included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects with COPD received at least 1 dose of BREO 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

**6-Month Trials:** The incidence of adverse reactions associated with BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n=1,224 and n=1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were white. They had a mean age of 62 years and an average smoking history of 44 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV<sub>1</sub> was 48% (range: 14% to 87%), the mean postbronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

In Trials 1 and 2, adverse reactions (≥3% incidence and more common than placebo) reported in subjects with COPD taking BREO 100/25 (n=410) (vilanterol 25 mcg [n=408]; fluticasone furoate [n=410]; or placebo [n=412]) were: nasopharyngitis 9% (10%, 8%, 8%); upper respiratory tract infection 7% (5%, 4%, 3%); headache 7% (9%, 7%, 5%); and oropharyngeal candidiasis 5% (2%, 3%, 2%). Oropharyngeal candidiasis includes oral candidiasis, candidiasis, and fungal oropharyngitis.

**12-Month Trials:** Long-term safety data is based on two 12-month trials (Trials 3 and 4; n=1,633 and n=1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were white. They had a mean age of 64 years and an average smoking history of 46 pack-years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV<sub>1</sub> was 45% (range: 12% to 91%), and the mean postbronchodilator FEV<sub>1</sub>/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions previously mentioned, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO 100/25 (n=806) for 12 months included back pain, pneumonia [see *Warnings and Precautions (5.5)*], bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

#### 6.2 Clinical Trials Experience in Asthma:

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

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

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis, 10% (7%, 7%); headache, 5% (4%, 4%); oropharyngeal pain, 2% (2%, 1%); oral candidiasis, 2% (2%, 0%); and dysphonia, 2% (1%, 0%). Oral candidiasis includes oral candidiasis and oropharyngeal candidiasis.

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

In Trial 2, adverse reactions (≥2% incidence) reported in subjects with asthma taking BREO 200/25 (n=346) (BREO 100/25 [n=346]

or fluticasone furoate 100 mcg [n=347]) were: headache, 8% (8%, 9%); nasopharyngitis, 7% (6%, 7%); influenza, 3% (3%, 1%); upper respiratory tract infection, 2% (2%, 3%); oropharyngeal pain, 2% (2%, 1%); sinusitis, 2% (1%, <1%); bronchitis, 2% (<1%, 2%); and cough, 1% (2%, 1%).

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

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

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

#### 6.3 Postmarketing Experience:

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.

**Cardiac Disorders:** Palpitations, tachycardia.

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

**Musculoskeletal and Connective Tissue Disorders:** Muscle spasms.

**Nervous System Disorders:** Tremor.

**Psychiatric Disorders:** Nervousness.

**Respiratory, Thoracic, and Mediastinal Disorders:**

Paradoxical bronchospasm.

### 7 DRUG INTERACTIONS

#### 7.1 Inhibitors of Cytochrome P450 3A4:

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

#### 7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:

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

#### 7.3 Beta-Adrenergic Receptor Blocking Agents:

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents

for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

#### 7.4 Non-Potassium-Sparing Diuretics:

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy:

**Teratogenic Effects:** Pregnancy Category C. There are no adequate and well-controlled trials with BREO in pregnant women. Corticosteroids and beta<sub>2</sub>-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO.

**Fluticasone Furoate and Vilanterol:** There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day).

**Fluticasone Furoate:** There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal doses up to 27 mcg/kg/day).

**Vilanterol:** There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal oral doses up to 10,000 mcg/kg/day).

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

#### 8.2 Labor and Delivery:

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

#### 8.3 Nursing Mothers:

It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and beta<sub>2</sub>-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

#### 8.4 Pediatric Use:

BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.

In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. [See *Clinical Studies* (14.2) of full prescribing information.] Adolescents aged 12 to 17 years made up 14% of the study population (n=281), with a mean exposure of 352 days for subjects in this age-group treated with BREO 100/25 (n=151) and 355 days for subjects in this age-group treated with fluticasone furoate 100 mcg (n=130). In this age-group, 10% of subjects treated with BREO 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age-group.

**Effects on Growth:** Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of

children and adolescents with ICS, including fluticasone furoate, on final adult height are not known. [See *Warnings and Precautions* (5.17); *Use in Special Populations* (8.4) of full prescribing information.]

#### 8.5 Geriatric Use:

Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of BREO for COPD included 2,508 subjects aged 65 and older and 564 subjects aged 75 and older. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

#### 8.6 Hepatic Impairment:

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

#### 8.7 Renal Impairment:

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

### 10 OVERDOSAGE

No human overdose data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdose for the individual components described below apply to BREO. Treatment of overdose consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdose.

#### 10.1 Fluticasone Furoate:

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

#### 10.2 Vilanterol:

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

### 17 PATIENT COUNSELING INFORMATION

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

#### Asthma-Related Death

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

#### Not for Acute Symptoms:

Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta<sub>2</sub>-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following: decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists; need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists; significant decrease in lung function as outlined by the physician.

Tell patients they should not stop therapy with BREO without physician/provider guidance since symptoms may recur after discontinuation.

#### Do Not Use Additional Long-acting Beta<sub>2</sub>-agonists:

Instruct patients not to use other LABA for COPD and asthma.

#### Local Effects:

Inform patients that localized infections with *Candida albicans*

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

#### Pneumonia:

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

#### Immunosuppression:

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

#### Hypercorticism and Adrenal Suppression:

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

#### Reduction in Bone Mineral Density:

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

#### Ocular Effects:

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

#### Risks Associated with Beta-agonist Therapy:

Inform patients of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

#### Hypersensitivity Reactions, Including Anaphylaxis:

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

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BREO ELLIPTA was developed in collaboration with Theravance



GlaxoSmithKline  
Research Triangle Park, NC 27709

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Revised 7/2016

BRE:7BR5



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Printed in USA. 804638R0 November 2016

# Corticosteroids reduce risks in elective extubation

BY BIANCA NOGRADY  
Frontline Medical News

FROM CHEST

**P**rophylactic corticosteroids before elective extubation could significantly reduce postextubation stridor and the incidence of reintubation, particularly in patients at high risk of airway obstruction, suggests a systematic review and meta-analysis.

While current guidelines for the management of tracheal extubation call for prophylactic use of corticosteroids in patients with airway compromise, Akira Kuriyama, MD, of Kurashiki Central Hospital in Japan, and coauthors noted that there is an outstanding question as to which patients are most likely to benefit.

Writing in the Feb. 20 online edition of CHEST, they reported on an analysis of 11 randomized, controlled trials of prophylactic corticosteroids given before elective extubation, involving 2,472 participants (CHEST. 2017 Feb 20. doi: 10.1016/j.chest.2017.02.017).

They found that the use of prophylactic corticosteroids was associated with a significant 57% reduction in the incidence of postextubation airway obstruction, laryngeal edema, or stridor, and a 58% reduction in reintubation rates, compared with placebo or no treatment.

A subgroup analysis showed that

the benefit in reduction of postextubation airway events was evident only in the six trials that selected patients at high risk of airway obstruction, identified by a cuff-leak test (relative risk, 0.34), and was not seen in trials with an unselected patient population. Similarly, the reduced incidence of reintubation was evident in trials of high-risk individuals (RR, 0.35) but not in the general patient population.

The authors noted that, while the latest systematic reviews had shown that corticosteroids reduce the incidence of postextubation stridor and reintubation, only one review examined the efficacy in high-risk populations and even then, it was a pooled subgroup analysis of only three trials.

“The numbers needed to prevent one episode of postextubation airway events and reintubation in individuals at high risk for postextubation airway obstruction were 5 (95% confidence interval, 4-7) and 16 (95% CI, 8-166) respectively,” they wrote, noting that routine administration of corticosteroids before elective extubation is not recommended.

“While the use of prophylactic corticosteroids was associated with few adverse events, it is reasonable to use the cuff-leak test as a screening method, and administer prophylactic steroids only to those who are at risk

## VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** A recent CHEST evidence-based guideline on liberation from mechanical ventilation suggested the administration of corticosteroids to high-risk patients failing a cuff-leak test in order to prevent re-intubation and avoid postextubation airway complications. Now, a systematic review by Kuriyama et al. published in CHEST has found evidence that high-risk patients failing a cuff-leak test have improved postextubation outcomes when given corticosteroids upon elective extubation. Both reviews are limited by a lack of consistency among the individual studies in terms of the protocol for performing the cuff-leak. Consensus for the optimal cuff-leak algorithm must be developed so that physicians can identify the at-risk populations.



of developing postextubation obstruction, given our study findings.”

Two of the six trials that identified high-risk individuals used a cuff-leak volume less than 24% of tidal volume during inflation, three used a cuff-leak volume of less than 110 mL, and one used a cuff-leak volume less than 25% of tidal volume.

“This potentially indicates that cuff-leak testing, while applied with varying cut-off values, might be able to select those at similar risk for airway obstruction and underlines the importance of screening for high-risk patients,” the authors said.

The researchers also noted that the longer patients were intubated, the lower the effect size of pro-

phylactic corticosteroids on both postextubation airway events and reintubation.

“Patients thus tended to benefit from prophylactic corticosteroids to prevent postextubation airway events and subsequent reintubation when the duration of mechanical ventilation was short,” they wrote.

The authors noted that the included trials did differ in terms of populations, corticosteroid protocols, and observation periods.

However, they pointed out that the statistical heterogeneity in their primary outcome analysis was due to the risk of postextubation airway obstruction.

The authors declared no conflicts of interest.

# Incompatible Type A plasma safe for resuscitation protocol

BY MICHELE G. SULLIVAN  
Frontline Medical News

HOLLYWOOD, FLA. – Incompatible Type A plasma appears to be a safe and effective part of an initial resuscitation protocol for trauma patients who need a massive transfusion.

There were no increases in morbidity, mortality, or transfusion-related acute lung injury among 120 patients who received Type A plasma, compared with those who got compatible plasma, Bryan C. Morse, MD, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

Type AB blood products are preferred for initial transfusions for trauma patients with unknown blood type. While type AB blood products are universally acceptable to patients, they are also in short supply. In an attempt to mitigate this shortage, some trauma centers are relying on anecdotal data, much drawn from real-life combat experience dating from World War II to present times, suggesting that Type A plasma is safe for initial resuscitation protocols.

But the body of data from well-constructed trials is small, said Dr. Morse of Emory University, Atlanta. Thus, EAST sponsored this retrospective registry study, which examined outcomes in 1,536 trauma patients who received plasma transfusions as part of a massive transfusion protocol from 2012 to 2016.

The primary endpoints were overall morbidity, and mortality at four time points: 6 and 24 hours, and 7 and 28 days. Eight trauma centers contributed data to the study.

The group was largely male (75%) with a mean age of 37 years. Patients were seriously injured, with a mean Injury Severity Score (ISS) of 25. About 60% suffered from blunt-force trauma. Among the entire group, 120 (8%) received incompatible type A plasma.

About 28% of patients (434) experienced an adverse event. These were numerically but not significantly more common among the incompatible A plasma group (35% vs. 28%;  $P = .14$ ). Events included acute respiratory distress syndrome (6% vs. 7.6%), thromboembolism (9% vs. 7%), pneumonia (19% vs. 15%), and acute kidney injury (8% each).

There were two cases of transfusion-related acute lung injury, both of which occurred in the compatible type A group.

Mortality was similar at every time point: 6 hours (16% vs. 15%), 24 hours (25% vs. 22%), 7 days (35% vs. 32%), and 28 days (38% vs. 35%).

A multivariate regression model controlled for treatment center, ISS, units of packed red cells given by 4 hours, mechanism of injury, Type A plasma incompatibility, and age.

In the morbidity analysis, only ISS and units of red blood cells at 4 hours were associated with a significant increase in risk (odds ratio, 1.02). Incompatible Type A plasma did not significantly increase the risk of morbidity.

In the mortality analysis, units of red cells, ISS, and age were significantly associated with increased risk. Again, incompatible Type A plasma did not significantly increase the risk of death.

Dr. Morse had no financial declaration.

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# LMWH cut venous thromboembolism risk

BY MICHELE G. SULLIVAN  
*Frontline Medical News*

HOLLYWOOD, FLA. – Low-molecular-weight heparin (LMWH) decreased the risk of venous thromboembolism in trauma patients significantly more than did unfractionated heparin, a large state database review has found.

It also was associated with a 37% decrease in overall mortality, compared with unfractionated heparin, Benjamin Jacobs, MD, said at the annual scientific assembly of the Eastern Association for the Surgery of Trauma.

“Given these data, we feel that LMWH should be the preferred prophylactic agent in patients with trauma,” said Dr. Jacobs of the University of Michigan, Ann Arbor. He extracted data describing thromboembolism prophylaxis among 37,868 trauma patients included in the Michigan Trauma Quality Improvement Program from 2012 to 2014. The patients were treated at 23 hospitals around the state. They received either unfractionated or LMWH as their only clot-preventing protocol. LMWH was given at either 40 mg every day or 30 mg twice a day. The comparator was unfractionated heparin at 5,000 U either two or three times a day. The preferred method was LMWH, which 83% of patients received, compared with 17% who got the unfractionated heparin. Most patients who got LMWH received the 40 mg/day dose (70%). Most who got unfractionated heparin received 5,000 U three times a day (87%).

Both types of heparin reduced the risk of all thromboembolic outcomes, and both doses of LMWH significantly reduced the risks. However, the 40-mg/day dose was significantly more effective than the twice-daily 30-mg dose in reducing the risk of venous thromboembolism (VTE) and deep vein thrombosis (DVT). Risk reductions for pulmonary thrombosis (PT) and mortality were not significantly different between the doses.

Compared with unfractionated heparin, LMWH decreased the risk of VTE by 33%; of PT by 48%; and of DVT by 27%. It also reduced the risk of death by 37%, compared with the unfractionated type.

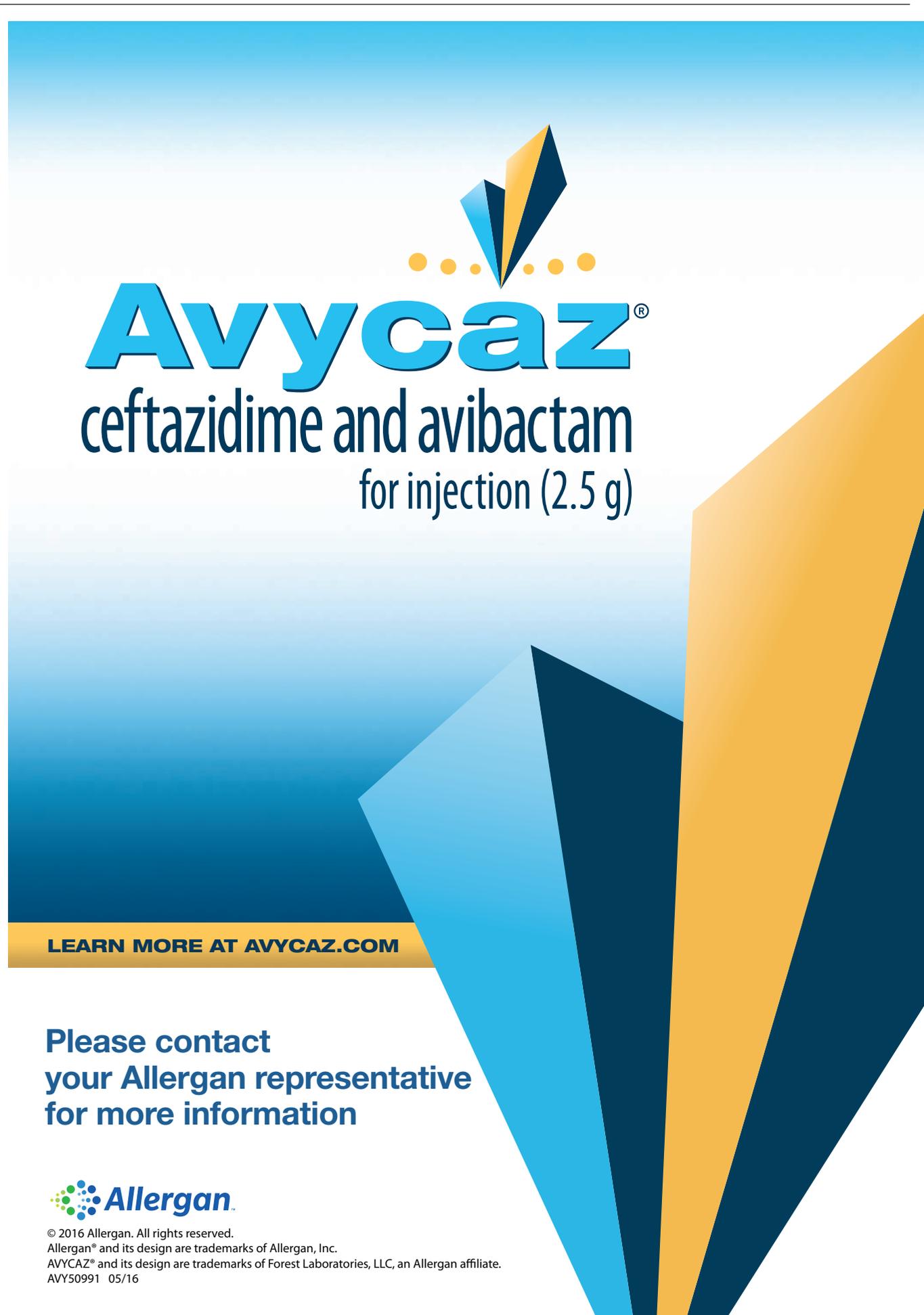
When Dr. Jacobs grouped the patients according to Injury Severity Score (ISS), he saw a consistently higher benefit among patients with lower scores. For example, LMWH significantly reduced the risk of PT by 59% in patients with an ISS of 5-14. In those with an ISS of 25 or higher, the drug was associated with a 20% increased

risk, although that wasn't statistically significant. There was a similar finding in DVT. LMWH reduced the risk by 18% in those with an ISS of 5-15, and by 50% among those with an score of 16-24 – both significant reductions.

Among those with an ISS of at least 25, the risk was 18% higher; although, again, it was not a significant finding. Curiously, the mortality benefit was stronger among sicker patients. The benefit was nonsignificant among

those with an ISS of less than 25 but for those above 25, the mortality risk reduction was a significant 45%.

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AVY50991 05/16

# Intensive ventilation precedes lesser complications

BY AMY KARON  
Frontline Medical News

**A**ddition of 10 cm H<sub>2</sub>O to positive end-expiratory volume (PEEP) during mechanical ventilation was followed by significantly lessened pulmonary complications in hospitalized patients who developed hypoxemia after cardiac surgery, participating in a single-center, randomized trial.

This “intensive” alveolar recruitment strategy yielded a median pulmonary complications score of 1.7 (interquartile range, 1.0-2.0), compared with 2.0 (IQR, 1.5-3.0) among patients who underwent ventilation with a PEEP of 20 cm H<sub>2</sub>O, Alcino Costa Leme, RRT, PhD, said at the International Symposium on Intensive Care and Emergency Medicine. The report was published simultaneously online March 21 in JAMA.

Intensive alveolar recruitment nearly doubled the odds of a lower pulmonary complications score (common odds ratio, 1.9; 95% confi-

dence interval, 1.2-2.8;  $P = .003$ ), Dr. Leme and his associates reported.

The study comprised 320 adults who developed hypoxemia immediately after undergoing elective cardiac surgery at the Heart Institute

(Incor) of the University of São Paulo. The median age of the patients was 62 years, and none had a history of lung disease. Pulmonary complications were scored between 0 (no signs or symptoms) and 5 (death), the

investigators noted (JAMA. 2017 Mar 21. doi: 10.1001/jama.2017.2297).

The intensive alveolar recruitment strategy consisted of three 60-second cycles of lung inflation with a positive end-expiratory pressure of 30 cm

## VIEW ON THE NEWS

### High PEEP for all?

**H**igh PEEP “not only recruits collapsed lung tissue, but can also lead to lung overdistension. If lung collapse is extensive, as in patients with ARDS [acute respiratory distress syndrome], and maybe also in patients with postoperative ARDS, the balance between benefit (i.e., recruitment of lung tissue), and harm (i.e., lung overdistension), tips toward benefit. If there is very little lung collapse, as in critically ill patients without ARDS or patients during surgery, this balance could go in the other direction.”

The clinical trial by Leme and his colleagues “provides another brick in the evidence wall of lung protection. However, it remains unclear which patients benefit most from ventilation with a high [positive end-expiratory pressure] level.”

*Ary Serpa Neto, MD, MSc, PhD, and Marcus J. Schultz, MD, PhD, are at the Academic Medical Center, Amsterdam. They reported having no conflicts of interest. These comments are from their editorial (JAMA. 2017 Mar 21. doi: 10.1001/jama.2017.2570).*

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

**TYVASO®**  
(treprostinil) INHALATION SOLUTION

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

**REMODULIN®**  
(treprostinil) Injection

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

**orenitram®  
treprostinil**  
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.

H<sub>2</sub>O, pressure-controlled ventilation, driving pressure of 15 cm H<sub>2</sub>O, respiratory rate of 15/min, inspiratory time of 1.5 seconds, and FIO<sub>2</sub> of 0.40. Between and after inflations, patients received assist-controlled or pressure-controlled ventilation, with driving pressures set to achieve a tidal volume of 6 mL/kg of predicted

body weight, an inspiratory time of 1 second, PEEP of 13 cm H<sub>2</sub>O, and minimum respiratory rate to maintain PaCO<sub>2</sub> between 35 and 45 mm Hg.

The “moderate strategy” consisted of three 30-second inflations under continuous positive airway pressure mode at 20 cm H<sub>2</sub>O and

FIO<sub>2</sub> of 0.60. Between and after inflations, patients received assist or control volume-controlled ventilation (decelerating-flow waveform), tidal volume of 6 mL/kg of predicted body weight, inspiratory time of 1 second, PEEP of 8 cm H<sub>2</sub>O, and FIO<sub>2</sub> of 0.60, at a minimum respiratory rate that main-

tained PaCO<sub>2</sub> at 35-45 mm Hg.

“[The] use of an intensive alveolar recruitment strategy compared with a moderate recruitment strategy resulted in less severe pulmonary complications during the hospital stay,” the investigators wrote. On average, intensively managed patients

*Continued on following page*

## TREATING PAH IS A MATTER OF URGENCY.<sup>1</sup> WHY WAIT TO INITIATE A PROSTACYCLIN ANALOGUE?

# CULTIVATE A CONTINUUM OF CARE WITH THE TREPROSTINIL SYSTEM

A range of prostacyclin analogues for cohesive PAH treatment over the course of disease.<sup>2-4</sup>

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- **Reach for Remodulin**—for the #1-prescribed parenteral PAH therapy<sup>5</sup>
- **Return to Orenitram**—for oral delivery in hemodynamically stable FC I and II Remodulin patients<sup>2</sup>

**Talk to your United Therapeutics representative for more information.**

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- Treprostinil is a pulmonary and systemic vasodilator. Concomitant administration of treprostinil 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 treprostinil relative to patients with normal hepatic function; therefore, treprostinil dosage should be titrated slowly in these patients

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

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CORPORATION  
**COMMITTED TO PAH**

Continued from previous page

had shorter stays in the hospital (10.9 vs. 12.4 days;  $P = .04$ ) and in the intensive care unit (3.8 vs. 4.8 days;  $P = .01$ ) than did moderately managed patients. Intensive management also was associated with lower rates of hospital mortality and barotrauma,

but the differences in these less common outcomes did not reach statistical significance.

“To our knowledge, this is the first study to show a significant effect of lung recruitment maneuvers on clinical outcomes, which objectively resulted in modest reductions in ICU and hospital length of stay,” the re-

searchers wrote. “This is especially noteworthy considering that the control group was also receiving protective lung ventilation with low [tidal volume] and moderate PEEP levels. Thus, the major difference between treatment groups was the intensity of lung recruitment.”

FAPESP (Fundação de Amparo e

Pesquisa do Estado de São Paulo) and FINEP (Financiadora de Estudos e Projetos) provided partial funding. Dr. Leme had no disclosures. Senior author Marcelo Britto Passos Amato, MD, PhD, disclosed research funding from Covidien/Medtronic, Dixtal Biomedica, and Timpel SA.

### 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.

# Dexmedetomidine improves sedation in sepsis

BY AMY KARON  
Frontline Medical News

Use of dexmedetomidine improved sedation among ventilated patients with sepsis, but did

not significantly cut mortality rates or increase ventilator-free days in a multicenter, open-label randomized controlled trial.

Twenty-eight days after the start of mechanical ventilation, cumulative

mortality rates were 23% among patients who received dexmedetomidine and 31% among those who did not (hazard ratio, 0.7; 95% confidence interval, 0.4-1.2;  $P = .2$ ), Yu Kawazoe, MD, PhD, and his associates reported

at the International Symposium on Intensive Care and Emergency Medicine. The report was simultaneously published in JAMA.

“The study may have identified a  
*Continued on following page*

  
**orenitram**<sup>®</sup>  
treprostiniil  
EXTENDED-RELEASE TABLETS

## BRIEF SUMMARY

The following is a brief summary of the full prescribing information for Orenitram<sup>®</sup> (treprostiniil) 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**—Treprostiniil 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 treprostiniil. 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 treprostiniil. Additionally, treprostiniil 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 treprostiniil at an infusion rate of 10 ng/kg/min.

## USE IN SPECIFIC POPULATIONS

**Pregnancy**—*Pregnancy Category C*. Animal reproductive studies with treprostiniil 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 treprostiniil treatment-related effects on labor and delivery were seen in animal studies.

**Nursing Mothers**—It is not known whether treprostiniil 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 treprostiniil 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.

Continued from previous page

clinically important benefit of dexmedetomidine – an 8% reduction in 28-day mortality – that did not demonstrate statistical significance ...” wrote Dr. Kawazoe of Tohoku University Graduate School of Medicine, Sendai, Japan. “Physicians may consider an 8% differ-

ence in 28-day mortality to be clinically significant, but this study was underpowered to detect this difference.”

Dexmedetomidine often is used for sedation during ventilation, but its effects on mortality and ventilator weaning are poorly understood, the researchers noted. However, this highly selective alpha<sub>2</sub>-adrenergic agonist

has been found to suppress inflammation and to protect organs, and “can improve patients’ ability to communicate pain compared with midazolam and propofol,” the researchers wrote. Therefore, they randomly assigned 201 patients with sepsis at eight intensive care units in Japan to receive sedation with or without dexmedeto-

midine. Both arms received fentanyl, propofol, and midazolam, dosed to achieve Richmond Agitation-Sedation Scale (RASS) scores of 0 (calm) during the day and –2 (lightly sedated) at night (JAMA. 2017 March 21. doi: 10.1001/jama.2017.2088).

The dexmedetomidine group spent  
Continued on following page



#### 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<sub>max</sub> 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 (TRIUMPH1) 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<sub>max</sub> 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 fluconazole (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.  
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www.tyvaso.com  
TYVShcpJun16

**United  
Therapeutics**  
CORPORATION

# A quarter of cultures were carbapenem-resistant

BY LUCAS FRANKI  
Frontline Medical News

Nearly one-quarter of *Klebsiella pneumoniae* cultures in a network of U.S. long-term acute

care hospitals are resistant to carbapenem, according to Jennifer H. Han, MD, and her associates.

From a sample of 3,846 *K. pneumoniae* cultures taken from 64 long-term acute care hospitals in 16 states, 946,

or 24.6%, of the cultures were carbapenem-resistant, and were taken from 821 patients. Just under 54% of CRKP isolates were taken from a respiratory source, with 37% coming from urine and the remaining 9.4% coming from

blood. Nearly all CRKP isolates were resistant to fluoroquinolones, and 59.2% were resistant to amikacin.

Respiratory failure was the most common comorbidity, occurring in nearly 40% of patients with CRKP. Just over 50% of CRKP patients had a central venous catheter, and 64.8% of patients had a tracheostomy. The median age of patients with CRKP was 72.

Of the 16 states from which cultures were taken, California had the highest rate of carbapenem resistance, with 45.5% of *K. pneumoniae* cultures showing resistance. Other states with high rates of CRKP included South Carolina, Kentucky, and Indiana.

“Given the chronically, critically ill population, with convergence of at-risk patients from multiple facilities, future studies of optimal infection prevention strategies are urgently needed for this setting. In addition, expansion of national surveillance efforts and improved communication between [long-term acute care hospitals] and acute care hospitals will be critical for reducing the continued emergence and dissemination of CRKP across the health care continuum,” Dr. Han and her associates concluded.

Find the full study in *Clinical Infectious Diseases* (doi: 10.1128/CID.1201.1545).  
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lfranki@frontlinemedcom.com

Continued from previous page

a median of 20 days off the ventilator, compared with 18 days for controls ( $P = .20$ ), the investigators reported. However, dexmedetomidine led to significantly higher rates of well-controlled sedation. The highest rate of well-controlled sedation (defined as having a RASS scores between  $-3$  and  $1$  throughout 1 day in the ICU) in treated patients was 58%, while the highest rate of well-controlled sedation in the control group was 39% ( $P = .01$ ). Rates of adverse events did not significantly differ between groups. Bradycardia was most common, affecting 7% of the intervention group and 2% of controls ( $P = .1$ ) the researchers said.

Hospira Japan provided partial funding with a grant to Wakayama Medical University, and helped design the study but was otherwise not involved in the research project. Dr. Kawazoe disclosed ties to Hospira Japan and Pfizer Japan. Three coinvestigators disclosed ties to Pfizer Japan, AbbVie, AstraZeneca, Daiichi Sankyo, and several other pharmaceutical companies. The other coinvestigators had no disclosures.

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 <sup>†</sup>	NA <sup>†</sup>	1	32
Leading to discontinuation	0	3	0	7

\*Based on prescriptions for narcotics, not actual use

<sup>†</sup>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
Diarhea	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.

# Some abnormal findings may be underemphasized

BY JENNIE SMITH  
Frontline Medical News

FROM CHEST

**A** reporting system for lung cancer screening with low-dose computed tomography may underemphasize important abnormal findings other than nodules, researchers say, potentially leading to missed malignancies.

The American College of Radiology Lung Imaging Reporting and Data System, or Lung-RADS, was introduced in 2014 to standardize reporting for low-dose CT findings and also to reduce false-positive rates, by applying tighter criteria that was used in the National Lung Screening Trial.

Lung-RADS does not have specific reporting categories for patients with isolated hilar and mediastinal adenopathy or pleural effusion in the absence of lung nodules, even though these can indicate malignancy. It does allow for the inclusion of what is called an “S” code to indicate clinically significant findings other than nodules.

In the March 2017 issue of CHEST, Hiren Mehta, MD, and his colleagues at the University of Florida in Gainesville, report on four cases from their center in which patients with these pathologies had their scans read as Lung-RADS category 1, indicating a less than 1% likelihood of malignancy. No S codes were added to their reports. Subsequent testing in these patients revealed cancers (CHEST. 2017 March;151[3]:525-26).

The four cases were:

- A 56-year-old male with hilar and

mediastinal adenopathy who was recommended for repeat screening at 12 months. The patient presented 6 months later with pneumonia; biopsy revealed large cell lung cancer.

- A 76-year-old male with paratracheal lymph nodes and a solitary subcarinal lymph node. A subsequent biopsy revealed adenocarcinoma.
- A 67-year-old male whose scan showed bulky hilar and mediastinal adenopathy. Subsequent testing revealed Hodgkin’s lymphoma.
- A 75-year-old female whose scan showed a small pleural effusion and no nodules. Repeat scanning at 1 year showed enlargement of the effusion and lung adenocarcinoma.

Dr. Mehta and colleagues noted in their analysis that Lung-RADS has not been studied prospectively in real practice settings and that the four cases – two of which involved delayed diagnosis – reveal “a significant limitation” of Lung-RADS.

“Based on our experience, we believe that particular caution should be exercised in reporting Lung-RADS 1 category for patients with adenopathy/pleural effusion with no lung nodules, as a majority of the lung cancer screening scans will be ordered by [primary care providers. As] with any new system, an ongoing evaluation of the performance of Lung-RADS should be conducted so that the sensitivity and mortality benefit seen in the [National Lung Screening Trial] is not compromised.

“We strongly believe, based on our experience with these 4 cases that

the new version of Lung-RADS 2.0 should [account for shortcomings of the current Lung-RADS] and have a separate category for findings that are highly suspicious for malignancy

but do not have an accompanying lung nodule,” they wrote.

The investigators did not disclose outside funding or conflicts of interest related to their findings.

## VIEW ON THE NEWS

**M. Patricia Rivera, MD, FCCP,**

**comments:** The authors are commended for reporting these four cases as they highlight potential pitfalls in lung cancer screening. However, while Lung-RADS reporting emphasizes lung nodules, it recognizes that intra and extrathoracic incidental findings are equally important and these findings should be assigned the letter S to the final interpretation. The



cases reported in this article should have been assigned a Lung-RADS 1S on the initial low-dose CT with recommendations from the reporting radiologist on management of the S findings. As highlighted by these cases, non-small cell lung cancer and lymphoma explained the nodes and pleural effusion. We must not forget that small cell lung cancer, comprising about 15% of all lung cancers, is not likely to present with a pulmonary nodule but rather with hilar and mediastinal adenopathy. We are not accustomed to diagnosing small cell lung cancer in early stages but one has to consider that this tumor may present early on with isolated

hilar or mediastinal node.

Interpretation of a LDCT scan should follow the same practice as interpretation of CT scans outside of screening, that is thorough evaluation for potential significant findings such as coronary artery calcifications, adrenal or renal lesions, effusion(s), ascites, adenopathy, etc. Furthermore, in the final interpretation of these scans, these findings should be clearly stated with recommendations for follow-up.

This report also highlights, in my opinion, the important responsibility of individual review of the LDCT by the provider(s) participating in a screening program. This, of course, may be more feasible for pulmonologists and surgeons who should have experience, gained through clinical practice, in interpretation of CT scans. Internists and primary care physicians who order LDCT most likely solely rely on the radiologist interpretation and recommendations, further highlighting the importance of accurate reporting with clear recommendations for follow-up not only of nodules but of incidental findings.

# Spread through air spaces portends lung SCC recurrence

BY RICHARD MARK KIRKNER  
Frontline Medical News

**F**irst described in 2015, tumor spread through air spaces is a recently recognized form of invasion in lung carcinoma, but it has not been well described in lung squamous cell carcinoma. However, a study out of Memorial Sloan-Kettering Cancer Center reports spread through air spaces (STAS) is one of the most significant histologic findings in lung squamous cell carcinoma (SCC).

In multivariable models for any recurrence and lung cancer-specific death, the researchers found that STAS was a significant independent predictor for both outcomes ( $P = .034$  and  $.016$ , respectively).

“We found that STAS in lung SCC was associated with p-stage, lymphatic and vascular invasion, necrosis, larger nuclear diameter, increased mitoses and high Ki-67 labeling index,” wrote lead author

*Continued on following page*

## VIEW ON THE NEWS

### Refining prognosis with careful exam

**S**TAS (spread through air spaces) has emerged as a harbinger of poor clinical behavior in adenocarcinoma of the lung. In this new manuscript, a team from Memorial Sloan-Kettering Cancer Center demonstrates that this phenomenon is evident in squamous cell cancer of the lung as well.

A few important take-home messages are worthy of particular note in this manuscript. The first is that STAS is fairly common, present in one-third of all patients with squamous cell cancer. The second is that STAS is correlated with other known indicators of aggressive behavior such as stage, vascular and lymphatic invasion, and a high Ki-67 labeling index. The third is that STAS is not restricted to one particular histological subtype of

squamous cell cancer. The fourth is that STAS is predictive of lung cancer-related recurrence and death, independent of other prognostic factors.

While the study needs to be replicated in other datasets, it demonstrates the power of careful pathologic examination in predicting tumor biology. The age-old concept deserves renewed emphasis in the current era of “Omics” of various kinds.

*Sai Yendamuri, MD, is professor and chair of the department of thoracic surgery at Roswell Park Cancer Institute in Buffalo, N.Y., and is an associate medical editor for Thoracic Surgery News. He has no relevant disclosures.*

Continued from previous page

Shaohua Lu, MD, and coauthors (J Thorac Oncol. 2017 Feb;12[2]:223-34). Their findings are based on an analysis of 445 patients who had resection for stage I-III SCC over a 10-year period ending in 2009.

The Sloan-Kettering Group previously reported that STAS was a predictor of recurrence in stage I lung adenocarcinoma patients who had a limited resection (J Thorac Oncol. 2015;10[5]:806-14), and others reported STAS was a clinically significant finding in the disease. In the latest study, Dr. Lu and colleagues set out to determine if STAS is associated with tumor aggressiveness in lung SCC by using a large cohort of patients who had lung SCC resection. The lung resections they studied are from the aforementioned 2015 study that used immunohistochemistry to confirm squamous differentiation in otherwise poorly differentiated tumors.

Two pathologists reviewed tumor slides and used Ki-67 staining to confirm squamous differentiation. The study population comprised 98% former smokers, and the median age was 71.3; 76% (336) were older than 65.

Dr. Lu and colleagues noted how STAS in lung SCC differs from its presentation in lung adenocarcinoma. "In contrast to lung adenocarcinoma, in which STAS can manifest as micropapillary clusters, solid nests or single cells, all STAS lesions in lung SCCs consist of solid tumor cell nests," they wrote.

They found that STAS was associated with a higher risk of recurrence in SCC patients who had lobectomy, but not sublobar resection, whereas in patients with lung adenocarcinoma STAS was associated with a high risk of recurrence if they had sublobar resection.

The study observed STAS in 132 patients (30%). With a median follow-up of 3.4 years, 61% (273) of all patients died in that time. STAS tumors were more aggressive in nature than were non-STAS tumors. Pathologic features strongly associated with STAS were lymphatic invasion (40% for STAS vs. 19% for non-STAS patients); vascular invasion (36% vs. 22%); larger tumor size (median 4 cm vs. 3 cm); higher Ki-67 labeling index (32% vs. 13%); and higher tumor stage (23% with p-stage I, 35% p-stage II, and 43% p-stage III), all significant differences. Patients with STAS also had a higher 5-year cumulative incidence of any recurrence (39% vs. 26%) and lung cancer-specific death (30% vs. 14%), both significant differences.

STAS has an "insidious pattern of tumor invasion" that can be difficult for pathologists to detect and requires the gathering of specimens that include the adjacent lung parenchyma, Dr. Lu and

colleagues said. They also dispelled the myth that STAS is an ex vivo artifact. "STAS is morphologically different from tissue floaters and contaminant or extraneous tissues that can lead to diagnostic errors," they said.

And while the study showed that STAS is an independent predictor of recurrence and cancer-specific death, it

was not predictive of overall survival – perhaps because most of the study population was over age 65 and were more likely to die from other causes rather than lung cancer. "We found a strong correlation between STAS and high-grade morphologic patterns such as nuclear size, nuclear atypia, mitotic count and Ki-67 labeling index, suggesting that

STAS is associated with tumor proliferation," Dr. Lu and coauthors said.

"Because we found STAS to show greater prognostic significance than lymphatic vascular and visceral pleural invasion," it may be appropriate for STAS to be recorded for lung cancer specimens in pathology reports, the researchers noted.

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## 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.

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TREAT NOW. SLOW PROGRESSION.

# EBUS scope, EUS-FNA similarly effective

BY DEEPAK CHITNIS  
Frontline Medical News

In an assessment of a patient for lung cancer, a procedure involving the insertion of an EBUS scope in

the esophagus – EUS-B-FNA – can achieve similarly accurate results as endoscopic ultrasound guided–fine-needle aspiration (EUS-FNA), according to a new study.

This finding could lead patients to

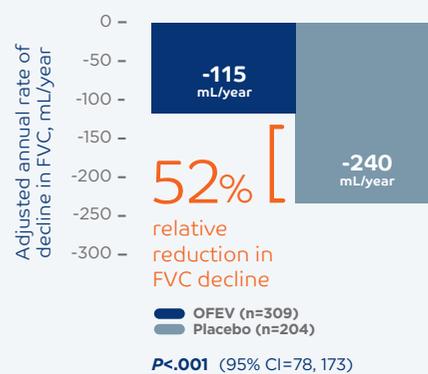
choose EUS-B-FNA over EUS-FNA – the standard of care for analyzing potential metastasis of the left adrenal glands (LAGs) – resulting in both time and cost savings for patients.

The current standard of care in-

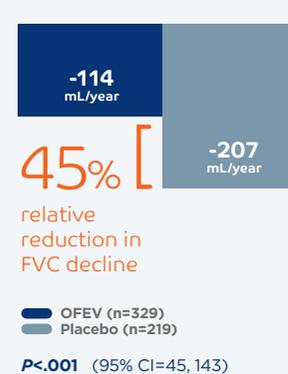
volves using an EBUS scope for complete mediastinal and hilar staging of lung cancer or, if present, a tumor. This is then followed by an assessment of the LAG by conducting ultrasound guided–fine-needle aspiration with a

## OFEV has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials<sup>3\*</sup>

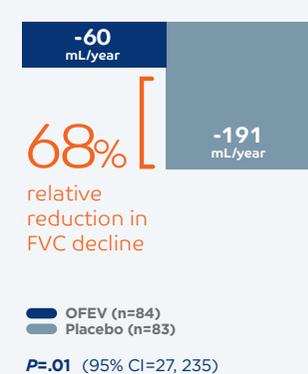
### INPULSIS<sup>®</sup>-1 (Study 2)<sup>3,4</sup>



### INPULSIS<sup>®</sup>-2 (Study 3)<sup>3,4</sup>



### TOMORROW (Study 1)<sup>3,5</sup>



CI, confidence interval.

\*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.<sup>3,4</sup>

## 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 FOOD<sup>3</sup>

Not shown at actual size

different scope. However, in this study, the investigators included an experimental procedure between those two steps, which involved advancing the EBUS scope into the patients' stomachs to find and assess the LAG. The idea is that, by using just one tool and technique rather than using an EBUS scope followed by the traditional EUS-

FNA (which involves using a second scope), both the patient and the provider save time and money.

"A recent report showed that LAG visualization using the EBUS scope was possible in 85% of patients," according to the authors of this study, including Joke T. Annema, MD, of the University of Amsterdam. Prior to this new

research, it was unknown to what extent a single EBUS scope adequately assess and sample the LAGs and how its performance related to the use of a conventional endoscopic ultrasound-guided scope (Lung Cancer. 2017. doi: org/10.1016/j.lungcan.2017.02.011).

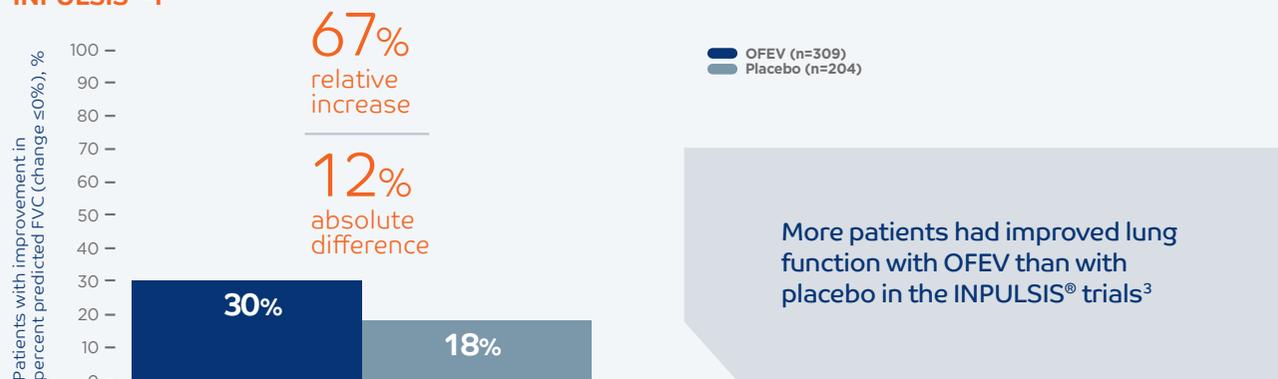
Dr. Annema and his coauthors recruited patients from four centers

– three in the Netherlands, one in Poland – and followed them prospectively. Patients with "(suspected) lung cancer [who] had an indication for both mediastinal lymph node and LAG sampling" were recruited for the study. The researchers followed 44 patients through final diagnosis to determine if they

*Continued on following page*

### 3 out of every 10 patients on OFEV showed an improvement ( $\leq 0\%$ decline) in lung function in the INPULSIS® trials<sup>3</sup>

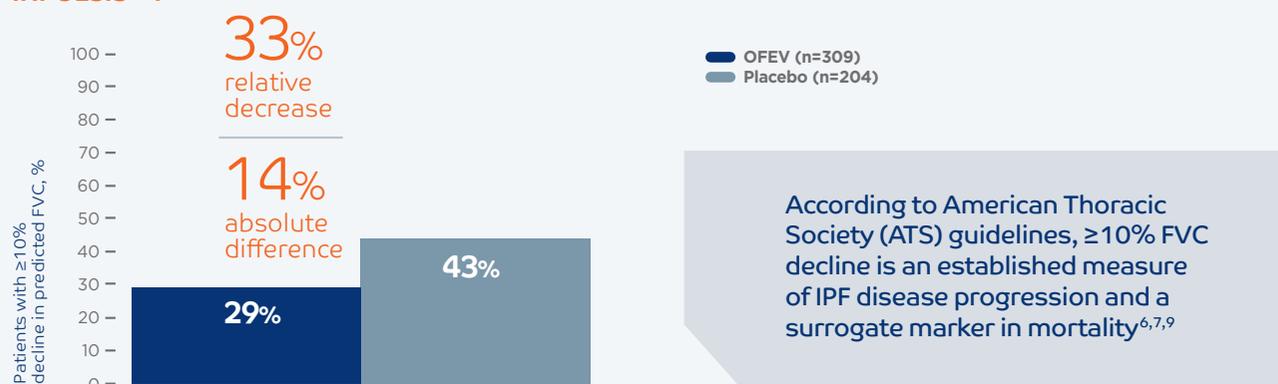
#### INPULSIS®-1<sup>3</sup>



- Similar results were observed in INPULSIS®-2<sup>3</sup>
- Lung function improvement is defined as a  $\leq 0\%$  decline in predicted FVC at 52 weeks, meaning patients' predicted FVC increased from baseline<sup>3</sup>

### LESS THAN ONE-THIRD OF PATIENTS ON OFEV HAD A MEANINGFUL DECLINE IN LUNG FUNCTION IN THE INPULSIS® TRIALS<sup>3,6-8</sup>

#### INPULSIS®-1<sup>3,6-8</sup>



- Similar results were observed in INPULSIS®-2<sup>3</sup>
- A meaningful decline is defined as patients with an absolute decline of  $\geq 10$  percentage points in predicted FVC at 52 weeks<sup>3,6-8</sup>

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

### IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

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

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



Continued from previous page

ultimately had lung cancer.

Subjects first received complete mediastinal and hilar staging of lung cancer and any present tumors via an EBUS and EUS-B procedure. Following an EBUS examination of the mediastinum, the EBUS scope was

retracted from the trachea and positioned into the esophagus for an examination of the mediastinal nodes. Then, the EBUS scope was advanced into the stomach for identification of the LAG. Afterward, the routine EUS-FNA was performed. LAG analysis across both methods involved visualizing the LAG and collecting an

adequate tissue sample for testing.

“In short, in order to locate the LAG, a structured three step approach was used according to the EUS assessment tool (EUS-AT): identification of the liver, abdominal aorta, coeliac trunk, left kidney, and LAG,” the authors noted. “By turning the EBUS scope clockwise from the liver, the abdominal aorta and

coeliac trunk are identified. By subsequently turning the EBUS scope gently in caudal direction, the left kidney and LAG are identified.”

Endoscopists then evaluated both procedures in each subject according to feasibility and practicability to determine if the findings of the experimental procedure were us-

## 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](http://www.OFEVhcp.com)—and fax it to one of the participating specialty pharmacies



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

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

### IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

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

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

### ADVERSE REACTIONS

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

### DRUG INTERACTIONS

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

### USE IN SPECIFIC POPULATIONS

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

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

OFPROFISIFEB16

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



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able. Finally, a cytologic exam was conducted, using Giemsa or Papanicolaou staining to determine if any present cancer had metastasized, and a final diagnosis was made.

LAG analysis had a success rate of 89% (39/44; 95% confidence interval, 76%-95%) for EUS-B-FNA, compared with 93% (41/44; 95% CI, 82%-98%)

for EUS-FNA. Similarly, when looking at the rate of sensitivity for LAG metastases, EUS-B had a rate of sensitivity for LAG metastases of at least 87% (95% CI, 65%-97%), while EUS-FNA was found to be at least 83% (95% CI, 62%-95%). Endoscopists were equally satisfied with both procedures in the "majority" of cases in this study.

"In [five] cases (11%), the EUS-B-FNA procedure was unsuccessful, due to the inability to make good contact of the ultrasound transducer and the stomach wall," the authors explained. "The conventional EUS scope is more stable as a result of the increased tube diameter. Another advantage of the conventional echo-endoscope is its

wider scanning angle. ... The conventional EUS scope is also longer than the EBUS scope, [but that] does not seem to be the limiting factor."

No funding source was disclosed for this study. The authors reported no relevant financial disclosures.

dchitnis@frontlinemedcom.com

## 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
<b>Gastrointestinal disorders</b>		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain <sup>a</sup>	15%	6%
Vomiting	12%	3%
<b>Hepatobiliary disorders</b>		
Liver enzyme elevation <sup>b</sup>	14%	3%
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	11%	5%
<b>Nervous systemic disorders</b>		
Headache	8%	5%
<b>Investigations</b>		
Weight decreased	10%	3%
<b>Vascular disorders</b>		
Hypertension <sup>c</sup>	5%	4%

<sup>a</sup> Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

<sup>b</sup> 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.

<sup>c</sup> 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

# Lung cancer screening a challenge to implement

BY JENNIE SMITH  
Frontline Medical News

**A** comprehensive lung cancer screening program carried out at Veterans Health Administra-

tion hospitals was taxing to implement and revealed a large number of patients with results requiring follow-up, though only 1.5% had cancers.

Investigators at eight VHA hospi-

tals, led by Linda S. Kinsinger, MD, of the VHA's National Center for Health Promotion and Disease Prevention in Durham, N.C., looked at records from about 93,000 primary care patients and identified 4,246 eligible for screen-

ing, based on age, medical history, and smoking history (JAMA Intern Med. 2017 Jan 30. doi: 10.1001/jamainternmed.2016.9022).

Approximately 58% of the eligible patients consented, and 2,106 underwent screening with low-dose computed tomography (LDCT) scans. The mean age of patients was 65 years, and 96% of patients were male. Nearly 60% of patients screened (1,257) had nodules, 1,184 patients (56.2%) required tracking, and 31 patients (1.5%) had lung cancer. The pilot study was developed in response to a 2013 recommendation from the U.S. Preventive Services Task Force favoring annual screening with LDCT scans in current or former heavy smokers between 55 and 80 years old. The recommendation sparked concerns about the practicality of implementing large-scale lung cancer screening, which Dr. Kinsinger and her colleagues' study seemed to underscore. For example, "creating electronic tools to capture the necessary clinical data in real time ... proved to be difficult, even with the VHA's highly regarded electronic medical record," the investigators wrote. A key measure used in the screening program – cigarette pack-years – was "not fully captured" in the system's EMR.

The investigators also noted that, if the eligibility criteria used in the pilot program were applied to the VHA nationwide, about 900,000 patients would be eligible for LDCT scan screening, and that fewer than 60% of patients in this study had consented. That meant that "accurately identifying these patients and discussing with them the benefits and harms of [screening] will take significant effort for primary care teams." Additionally, the required follow-up "may stress the capacity" of radiology and pulmonology services, they said. Finally, "primary care will need to be involved in deciding which incidental findings need further evaluation. These clinical efforts will require coordination and communication among clinical services and between patients and staff, and dedicated coordinators will need to be hired," the investigators said.

The authors noted that their findings might not be generalizable to non-VHA health care systems. The experience of the VHA, "owing to its central organizational structure, may represent a best-case scenario," they wrote.

The Veterans Health Administration funded the study. Two of its coauthors reported commercial conflicts of interest; one of those disclosed a grant application to the Bristol-Myers Squibb Foundation related to the screening.

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

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

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

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

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

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Rx only



# Bill would limit noneconomic damages to \$250,000

BY ALICIA GALLEGOS  
Frontline Medical News

New legislation headed to the House floor could mean legal relief for health providers in the form of capped damages and a tighter time frame for lawsuits.

The House Judiciary Committee passed the Protecting Access to Care Act of 2017 (H.R. 1215) in February by a vote of 18-17. The bill, modeled after California's Medical Injury Compensation Reform Act (MICRA), would limit noneconomic damages in medical malpractice cases to \$250,000, restrict contingency fees charged by attorneys, and enforce a 3-year statute of limitations for liability lawsuits from the date of alleged injury. The bill also includes a "fair share" rule in which defendants are liable only for the damages in direct proportion to their percentage of responsibility.

The bill is the first significant medical professional liability reform legislation to be approved by the committee since 2011, said Brian K. Atchinson, president and CEO of PIAA, a national trade association for medical liability insurers.

"Unlike previous federal bills, the bill is focused solely on health care professionals and entities, includes detailed flexibility for states for all its reforms, and is linked with the expenditure of federal dollars to address states' rights concerns," Mr. Atchinson said in a statement. "H.R. 1215 will help ensure fair and timely compensation to injured patients, improve access to patient care, and promote affordable and accessible medical liability insurance coverage."

The proposed statute would apply to any patient who receives medical care provided via a federal

program, such as Medicare or Medicaid, or via a subsidy or tax benefit, such as coverage purchased under the Affordable Care Act or a future replacement. Medical care paid by employer health plans would fall under the legislation's umbrella since insurance premiums receive federal tax exemptions. The bill would not preempt state medical malpractice laws that impose damage caps, whether higher or lower than \$250,000, nor would the legislation affect the availability of economic damages, according to bill language.

As part of the H.R. 1215, courts could limit how much attorneys receive from a patient's ultimate award. Specifically, courts would have the power to restrict payments from a plaintiff's damage recovery to an attorney who claims a financial stake in the outcome by virtue of a contingent fee.

If enacted, the bill would work to reduce the practice of defensive medicine and save taxpayer dollars, while increasing access to health care, said House Judiciary Committee Chair Bob Goodlatte (R-Va.).

"The Protecting Access to Care Act will help keep the rising costs of health care from being passed along to the American people," Rep. Goodlatte said in a statement. "The Congressional Budget Office estimates that the reforms contained in the bill would lower health care costs by tens of billions of dollars."

Public Citizen, a consumer rights group, criti-

cized the legislation as misleading to consumers and harmful to patients.

"Proposals to shield providers from liability are nothing but a giveaway to industry," Lisa Gilbert, director of Public Citizen's Congress Watch, said in a statement. "Members supporting this bill would further harm those who are suffering from doctors' mistakes and abandon the GOP's supposedly unwavering commitment to state's rights."

Jeffrey Segal, MD, a neurosurgeon and attorney, said the bill faces an uphill climb and may not make it very far.

The question is whether the legislation can pass via the budget reconciliation process (requiring only a simple majority in the Senate) or whether it would be presented outside of that process and would need 60 votes, he said in an interview.

"There are so many moving parts to this bill, I think the likelihood of its being passed as is is low," said Dr. Segal, founder of Medical Justice, a company that works to deter frivolous medical malpractice lawsuits. "The biggest challenge will be whether the Republicans have to get eight Democratic senators to join the bill. To make it more palatable, something will need to give. Such provisions on tort reform are likely to be the first items offered for sacrifice."



REP. GOODLATTE



DR. SEGAL

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On Twitter @legal\_med

## House leaders 'came up short' in effort to kill Obamacare

BY MARY AGNES CAREY,  
KAISER HEALTH NEWS

Despite days of intense negotiations and last-minute concessions to win over wavering GOP conservatives and moderates, House Republican leaders failed to secure enough support to pass their plan to repeal and replace the Affordable Care Act.

House Speaker Paul Ryan pulled the bill from consideration after he rushed to the White House to tell President Donald Trump that there weren't the 216 votes necessary for passage.

"We came really close today, but we came up short," he told reporters at a hastily called news conference.

When pressed about what happens to the federal health law, he added, "Obamacare is the law of the land. ... We're going to be living with Obamacare for the foreseeable future."

President Trump laid the blame at the feet of Democrats, complaining that not one was willing to help Republicans on the measure, and he warned again that the Obamacare

insurance markets are in serious danger. "Bad things are going to happen to Obamacare," he told reporters at the White House. "There's not much you can do to help it. I've been saying that for a year and a half. I said, look, eventually, it's not sustainable. The insurance companies are leaving."

But he said the collapse of the bill might allow Republicans and Democrats to work on a replacement. "I honestly believe the Democrats will come to us and say, 'Look, let's get together and get a great health care bill or plan that's really great for the people of our country,'" he said.

Rep. Ryan originally had hoped to hold a floor vote on the measure March 23 – timed to coincide with the 7th anniversary of the ACA – but decided to delay that effort because GOP leaders didn't have enough "yes" votes. The House was in session March 24, before his announcement, while members debated the bill.

House Democratic leader Nancy Pelosi (Calif.) said the speaker's deci-

sion to pull the bill "is pretty exciting for us ... a victory for the Affordable Care Act, more importantly for the American people."

The legislation was damaged by a variety of issues raised by competing factions of the party. Many members were nervous about reports by the Congressional Budget Office showing that the bill would lead eventually to 24 million people losing insurance, while some moderate Republicans worried that ending the ACA's Medicaid expansion would hurt low-income Americans.

At the same time, conservatives, especially the hard-right House Freedom Caucus that often has needled party leaders, complained that the bill kept too much of the ACA structure in place. They wanted a straight repeal of Obamacare, but party leaders said that couldn't pass the Senate, where Republicans don't have enough votes to stop a filibuster. They were hoping to use a complicated legislative strategy called budget reconciliation that would allow

them to repeal parts of the ACA that affect only federal spending.

The decision came after a chaotic week of negotiations, as party leaders sought to woo more conservatives. The president lobbied 120 members through personal meetings or phone calls, according to a count provided by his spokesman, Sean Spicer. "The president and the team here have left everything on the field," Mr. Spicer said.

On the evening of March 23, Mr. Trump dispatched Office of Management and Budget Director Mick Mulvaney to tell his former House GOP colleagues that the president wanted a vote on March 24. It was time to move on to other priorities, including tax reform, he told House Republicans.

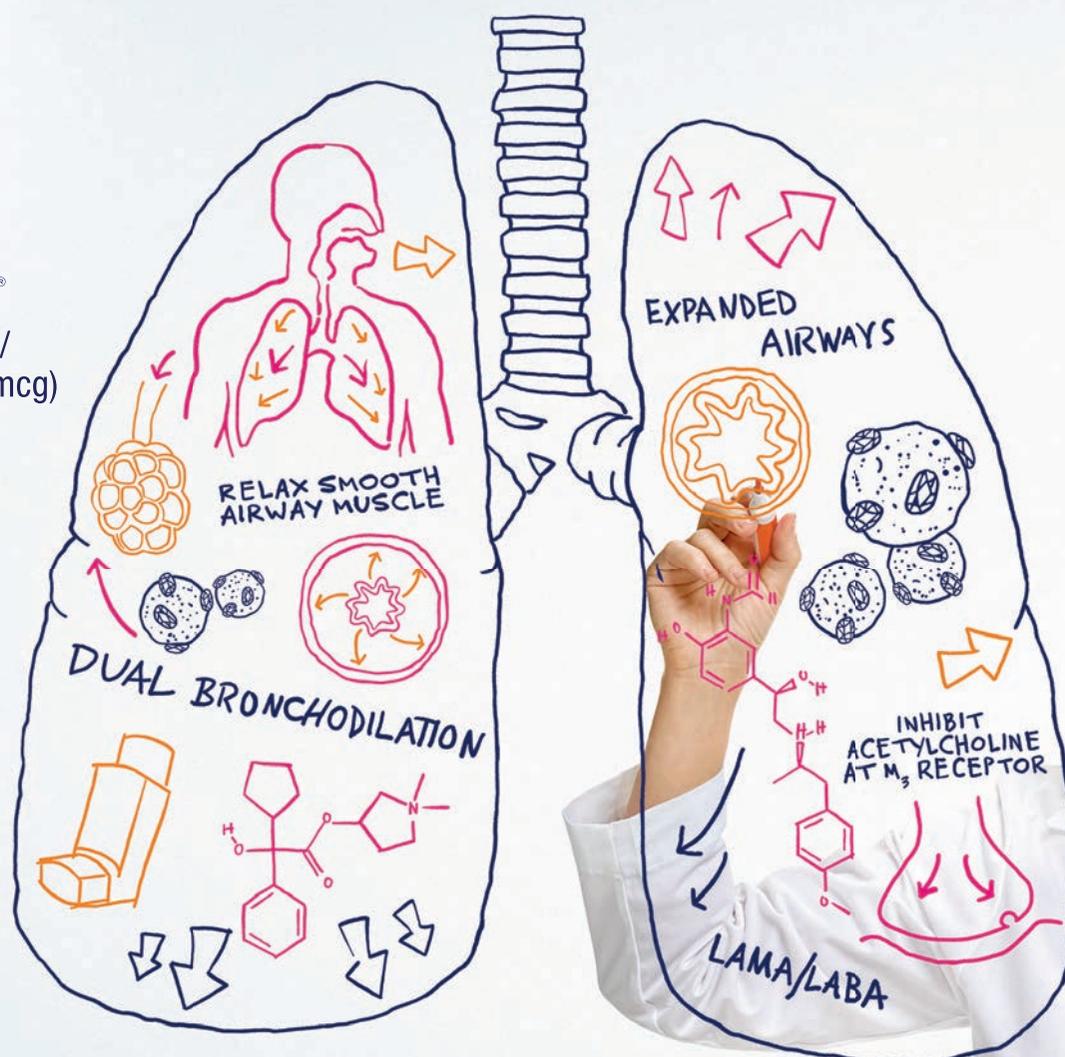
"He said the president needs this; the president has said he wants a vote tomorrow, up or down. If for any reason it goes down, we're just going to move forward with additional parts of his agenda. This is our

Continued on page 36



**BEVESPI**  
AEROSPHERE®

(glycopyrrolate 9 mcg/  
formoterol fumarate 4.8 mcg)  
Inhalation Aerosol



**BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD.**

**It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.**

**Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.**

## IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

**WARNING: Long-acting beta<sub>2</sub>-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.**

**The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.**

**CONTRAINDICATION:** All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. BEVESPI is contraindicated in patients with a hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product.

## WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting beta<sub>2</sub>-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically

significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

**ADVERSE REACTIONS:** The most common adverse reactions with BEVESPI (≥2% and more common than

FOR THE MAINTENANCE TREATMENT OF COPD

# DUAL BRONCHODILATION, DOWN TO A SCIENCE

## INTELLIGENT FORMULATION\*

Intelligent formulation for a pMDI using patented CO-SUSPENSION™ Delivery Technology<sup>1</sup>

## MAXIMIZE BRONCHODILATION<sup>†</sup>

Improved lung function<sup>†</sup> vs placebo including<sup>1</sup>

- 150-mL improvement in predose FEV<sub>1</sub> at 24 weeks
- Nearly a 300-mL improvement in peak FEV<sub>1</sub> at 24 weeks
- Nearly a 200-mL improvement in FEV<sub>1</sub> at 5 minutes on Day 1

Adverse reactions with BEVESPI AEROSPHERE with a  $\geq 2\%$  incidence and more common than placebo were urinary tract infection and cough.<sup>1</sup>

**BEVESPI AEROSPHERE is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms. It is not for the treatment of asthma.**

\*BEVESPI AEROSPHERE is a pMDI containing the LAMA glycopyrrolate and LABA formoterol fumarate, along with phospholipid porous particles that form the co-suspension with the micronized drug crystals.<sup>1</sup>

<sup>†</sup>Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials.<sup>1,3</sup>

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placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

### DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non-potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta<sub>2</sub>-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents

- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

**INDICATION:** BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting beta<sub>2</sub>-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

**LIMITATION OF USE:** Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

*You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.FDA.gov/medwatch](http://www.FDA.gov/medwatch) or call 1-800-FDA-1088.*

<sup>†</sup>Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). The primary endpoint was change from baseline in trough FEV<sub>1</sub> at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1;  $P < 0.0001$  for all treatment comparisons.<sup>1,2</sup> Statistically significant results were also seen in Trial 2.<sup>1,3</sup>

**References:** **1.** BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2016. **2.** Data on File, 3236300, AZPLP. **3.** Data on File, 3236400, AZPLP.

AstraZeneca 

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## BEVESPI AEROSPHERE™

(glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use

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

### WARNING: ASTHMA-RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. [see Warnings and Precautions (5.1) in the full Prescribing Information]

### INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

**Important Limitation of Use:** BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma [see Warnings and Precautions (5.1, 5.2) in the full Prescribing Information].

### DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

### CONTRAINDICATIONS

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions (5.1) in the full Prescribing Information]. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product [see Warnings and Precautions (5.5) in the full Prescribing Information].

### WARNINGS AND PRECAUTIONS

#### Asthma-Related Death

Data from a large placebo-controlled trial in subjects with asthma showed that LABAs may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABAs.

A 28-week, placebo-controlled US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted. The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

#### Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta<sub>2</sub>-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta<sub>2</sub>-agonist and instruct the patient on how it should be used. Increasing inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective, or the patient needs more inhalations of short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

#### Excessive Use of BEVESPI and Use with Other Long-Acting Beta<sub>2</sub>-Agonists

As with other inhaled medicines containing beta<sub>2</sub>-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason [see Drug Interactions (7.1) in the full Prescribing Information].

#### Paradoxical Bronchospasm

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

### Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

### Cardiovascular Effects

Formoterol fumarate, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms [see Clinical Pharmacology (12.2) in the full Prescribing Information]. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

### Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

### Hypokalemia and Hyperglycemia

Beta<sub>2</sub>-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. Beta<sub>2</sub>-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

### Worsening of Narrow-Angle Glaucoma

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

### Worsening of Urinary Retention

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

### ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma [see Boxed Warning and Warnings and Precautions (5.1) in the full Prescribing Information].

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Paradoxical bronchospasm [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Hypersensitivity reactions [see Contraindications (4), Warnings and Precautions (5.5) in the full Prescribing Information]
- Cardiovascular effects [see Warnings and Precautions (5.6) in the full Prescribing Information]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.9) in the full Prescribing Information]
- Worsening of urinary retention [see Warnings and Precautions (5.10) in the full Prescribing Information]

### Clinical Trials Experience

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

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week lung function trials, one long-term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least 1 dose of BEVESPI AEROSPHERE. The safety data described below are based on the two 24-week trials and the one 28-week long-term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

#### 24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

**Table 1 - Adverse Reactions with BEVESPI AEROSPHERE ≥2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease**

Adverse Reaction	BEVESPI AEROSPHERE (n=1036) %	Glycopyrrolate 18 mcg BID (n=890) %	Formoterol Fumarate 9.6 mcg BID (n=890) %	Placebo (n=443) %
Respiratory, thoracic, and mediastinal disorders				
Cough	4.0	3.0	2.7	2.7
Infections and infestation				
Urinary tract infection	2.6	1.8	1.5	2.3

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

**Long-Term Safety Extension Trial**

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of up to 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg administered twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

**Additional Adverse Reactions:** Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

**DRUG INTERACTIONS**

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

**Adrenergic Drugs**

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol, a component of BEVESPI AEROSPHERE, may be potentiated [see *Warnings and Precautions (5.3) in the full Prescribing Information*].

**Xanthine Derivatives, Steroids, or Diuretics**

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta<sub>2</sub> adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

**Non-Potassium Sparing Diuretics**

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta<sub>2</sub>-agonists, especially when the recommended dose of the beta<sub>2</sub>-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

**Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs**

BEVESPI AEROSPHERE, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

**Beta-Blockers**

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta<sub>2</sub>-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

**Anticholinergics**

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of BEVESPI AEROSPHERE with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions (5.9, 5.10) and Adverse Reactions (6) in the full Prescribing Information*].

**USE IN SPECIFIC POPULATIONS****Pregnancy****Teratogenic Effects:**

Pregnancy Category C. There are no adequate and well-controlled trials of BEVESPI AEROSPHERE or its individual components, glycopyrrolate and formoterol fumarate, in pregnant women. Because animal reproduction studies are not always predictive of human response, BEVESPI AEROSPHERE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BEVESPI AEROSPHERE.

**Glycopyrrolate:** There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m<sup>2</sup> basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal intramuscular injection dose of 0.5 mg/kg in rabbits).

Single-dose studies in humans found that very small amounts of glycopyrrolate passed the placental barrier.

**Formoterol Fumarate:** Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHDID (on a mg/m<sup>2</sup> basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHDID (on a mg/m<sup>2</sup> basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHDID (on a mg/m<sup>2</sup> basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHDID (on a mg/m<sup>2</sup> basis at maternal inhalation doses up to 1.2 mg/kg/day in rats).

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m<sup>2</sup> basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m<sup>2</sup> basis at maternal oral doses up to 3.5 mg/kg/day).

**Labor and Delivery**

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because beta<sub>2</sub>-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

**Nursing Mothers**

It is not known whether BEVESPI AEROSPHERE is excreted in human milk. Because many drugs are excreted in human milk and because formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, has been detected in the milk of lactating rats, caution should be exercised when BEVESPI AEROSPHERE is administered to a nursing woman. Since there are no data from controlled trials on the use of BEVESPI AEROSPHERE by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue BEVESPI AEROSPHERE, taking into account the importance of BEVESPI AEROSPHERE to the mother.

**Pediatric Use**

BEVESPI AEROSPHERE is not indicated for use in children. The safety and effectiveness of BEVESPI AEROSPHERE in the pediatric population have not been established.

**Geriatric Use**

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 290 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Hepatic Impairment**

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with hepatic disease should be closely monitored.

**Renal Impairment**

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m<sup>2</sup>) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

**OVERDOSAGE**

No cases of overdose have been reported with BEVESPI AEROSPHERE. BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuation of BEVESPI AEROSPHERE together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. Cardiac monitoring is recommended in case of overdosage.

**Glycopyrrolate**

High doses of glycopyrrolate, a component of BEVESPI AEROSPHERE, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. However, there were no systemic anticholinergic adverse effects following single inhaled doses up to 144 mcg in subjects with COPD.

**Formoterol Fumarate**

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta<sub>2</sub>-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

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Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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moment in time,” Rep. Chris Collins (R-N.Y.), a loyal Trump ally, told reporters late on March 23. “If it doesn’t pass, we’re moving beyond health care. ... We are done negotiating.”

Trump’s edict clearly irked some lawmakers, including the Freedom Caucus chairman, Rep. Mark Meadows (R-N.C), whose group of more than two dozen members represented the strongest bloc against the measure.

“Anytime you don’t have 216 votes, negotiations are not totally over,” he told reporters who had surrounded him in a Capitol basement hallway as he headed in to the party’s caucus meeting.

President Trump, Speaker Ryan, and other GOP lawmakers tweaked their initial package in a variety of ways to win over both conservatives and moderates. But every time one change was made to win votes in one camp, it repelled support in another.

The White House on March 23 accepted conservatives’ demands that the legislation strip federal guarantees of essential health benefits from insurance policies. But that was another problem for moderates, and Democrats suggested the provision would not survive in the Senate.



Republican moderates in the House – as well as the Senate – objected to the bill’s provisions that would shift Medicaid from an open-ended entitlement to a set amount of funding for states that also would give governors and state lawmakers more flexibility over the program. Moderates also were concerned that the package’s tax credits would not be generous enough to

help older Americans – who could be charged five times more for coverage than would their younger counterparts – afford coverage.

The House package also lost the support of key GOP allies, including the Club for Growth and Heritage Action. Physician, patient, and hospital groups also opposed it.

But Rep. Ryan’s comments made clear how difficult this decision was.

“This is a disappointing day for us,” he said. “Doing big things is hard. All of us. All of us – myself included – we will need time to reflect on how we got to this moment, what we could have done to do it better.”

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

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# Hospitalizations fell after rotavirus vaccine, PCVs

BY DAN WATSON  
Frontline Medical News

Vaccination programs targeting rotavirus and pneumonia in children younger than 2 years both contributed to a “rapid and considerable” decline in the hospital burden of pediatric patients, both in relation to those diseases and overall, according to an observational study.

Three vaccines were added to the National Immunization Plan in Israel within a 1.5-year interval, between July 2009 and January 2011: rotavirus vaccine and the 7-valent and 13-valent pneumococcal conjugate vaccines (PCV). Researchers studied the population at the Soroka University Medical Center in Beer Sheva, Israel, which was split roughly 50/50 between Jewish children and Bedouin Muslim children.

“The socioeconomic conditions and lifestyles of the two populations differ and social contacts between them, especially between children, are uncommon. However, both have access to the same medical services,” wrote Shalom Ben-Shimol, MD, of Ben-Gurion University of the Negev, Beer Sheva, and coauthors (J Pediatr. 2017 Mar;182:253-9.e2).

The rates of rotavirus gastroenteritis, nonrotavirus gastroenteritis, alveolar pneumonia, and nonalveolar lower respiratory tract infections in the 37,591 hospitalized children younger than 2 years de-

clined by 78%, 21%, 46%, and 7%, respectively, over the course of the study period. Outpatient ED visits for the same diseases declined 80%, 16%, 67%, and 13%, respectively.

The results are more evidence that rotavirus vaccine can help prevent diarrhea not caused by rotavirus and, similarly, that PCV can help prevent lower respiratory tract infections not caused by pneumococci.

Overall, hospitalizations and outpatient ED visits also declined significantly, by 11% and 12%, respectively.

“The impact of [rotavirus vaccine] and PCV may not be limited to prevention of diarrhea and respiratory disease, respectively. In one study, it was suggested that diarrhea may increase the risk of subsequent pneumonia in young children, pointing to potential synergistic benefits” of the vaccines, the authors wrote (Am J Epidemiol. 2005;162[10]:999-1007).

The study was supported by Merck Sharp & Dohme and Pfizer. Authors received speaker fees, research support, and consulting fees from those companies and from GlaxoSmithKline.

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# Unvaccinated first hit in pertussis outbreak

BY LUCAS FRANKI  
Frontline Medical News

During a 2012 pertussis outbreak in Oregon, unvaccinated or poorly vaccinated children were affected significantly earlier than fully vaccinated children were, according to Steve G. Robison, MPH, and

Juventila Liko, MD, MPH, from the Immunization Program, Oregon Health Authority, Portland.

A total of 351 pertussis cases in children aged 2 months to 10 years were reported in Portland and the upper Willamette Valley from Jan.

1 to Nov. 1, 2012. Children who were unvaccinated accounted for 76 (22%) of the reported cases, and children who were poorly vaccinated

accounted for 50 of the 275 (18%) cases in vaccinated children.

The median date of onset for unvaccinated and poorly vaccinated children was 117 days after Jan. 1, and the median date of onset for fully vaccinated children was 158 days after Jan. 1.

Mean date of onset was 133 days and 159 days after Jan. 1, respectively. In zip codes with both unvaccinated and vaccinated cases, children who were unvaccinated were 3.2 times more likely to have an earlier onset date.

“Diseases such as pertussis may spread across areas through the choice of parents to not immunize or to limit immunizations. Once locally present, pertussis will spread to the unimmunized and vulnerable, who in turn through the weight of exposure, may then ignite a wider outbreak in vaccinated populations,” the investigators noted.

Find the full study in the Journal of Pediatrics (doi: 10.1016/j.jpeds.2016.12.047).

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## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** These two articles represent the importance of vaccinations and their impact on the health of children worldwide. It is important to advocate locally and on a national level, no matter what the political climate is, for improvement in vaccination rates and vaccine research.



KATARZYNA BIALASIEWICZ/THINKSTOCK

# Pneumococcal conjugate vaccine resulted in a 95% decline in *Streptococcus pneumoniae* bacteremia

BY HEIDI SPLETE  
Frontline Medical News

Routine use of the 13-valent pneumococcal conjugate vaccine (PCV13) reduced the incidence of *Streptococcus pneumoniae* bacteremia by 95% from a time period before to a time period after the vaccine was implemented, based on a review of more than 57,000 blood cultures from children aged 3-36 months.

Kaiser Permanente implemented universal immunization with PCV13 in June 2010. “Initial trends through 2012 demonstrated continued decline in pneumococcal infections, with the biggest impact in children less than 5 years old,” wrote Tara Greenhow, MD, of Kaiser Permanente North-

ern California, San Francisco, and her colleagues.

The researchers conducted a retrospective cohort study of 57,733 blood cultures collected between Sept. 1, 1998, and Aug. 31, 2014, from previously healthy children aged 3-36 months seen in a single emergency department (Pediatrics. 2017 Mar 10. doi: 10.1542/peds.2016-2098).

Overall, the incidence of *S. pneumoniae* bacteremia declined from 74.5 per 100,000 children during the period before PCV7 (1998-1999) to 3.5 per 100,000 children during a period after routine use of PCV13 (2013-2014). The annual number of bacteremia cases from any cause dropped by 78% between these two time periods.

As bacteremia caused by pneumococci decreased, 77% of cases in the post-PCV13 time

period were caused by *Escherichia coli*, *Salmonella spp.*, and *Staphylococcus aureus*. “A total of 76% of bacteremia occurred with a source, including 34% urinary tract infections, 17% gastroenteritis, 8% pneumonias, 8% osteomyelitis, 6% skin and soft tissue infections, and 3% other,” Dr. Greenhow and her associates reported.

The large population of the Kaiser Permanente system supports the accuracy of the now rare incidence of bacteremia in young children, the researchers noted. However, “because bacteremia in the post-PCV13 era is more likely to occur with a source, a focused examination should be performed and appropriate studies should be obtained at the time of a blood culture collection,” they said.

# CRITICAL CARE COMMENTARY: Sepsis resuscitation in a post-EGDT age

BY LYNDSEY W. HEAD, MD, AND  
CRAIG M. COOPERSMITH, MD

Critical care – like all of medicine – is evolving at a rapid pace. In the relatively recent past, we moved from an era of consensus-based (if thinking optimistically) or opinion-based (if being less charitable) medicine to an era of evidence-based medicine. Despite the many valid concerns about ubiqui-



DR. HEAD



DR. COOPERSMITH

tous adoption of evidence-based medicine, there is little doubt that, on average, an aggregate population managed according to the best available literature does better than one managed solely on widely varying physician expertise. At the same time, there is no doubt that one size does not fit all, and in applying evidence-based protocols to all patients equally, we are helping many, having no effect on many, and are harming some. This has led to a still ongoing transition into an era of precision medicine where each patient gets the best care specifically for them. While the intellectual appeal of personalized therapy is obviously immense, the tools with which to do so currently remain relatively limited.

The approach to sepsis resuscitation is emblematic of the challenges and opportunities of the evolution in this transition. There was no standardized approach to early sepsis resuscitation in the 20th century, and mortality from the disease approached 50% in many studies. This changed in 2001 with the publication of the landmark early-goal-directed therapy (EGDT) trial (Rivers et al. *N Engl J Med*. 2001;345[19]:1368). This single center trial demonstrated a dramatic 16% absolute decrease in mortality secondary to usage of an aggressive protocol for sepsis resuscitation within the first 6 hours after presentation to the ED. In addition to early cultures and antibiotic therapy in patients randomized to both EGDT and “usual care,” EGDT involved a number of mandatory elements, including placing both an arterial catheter and a central venous

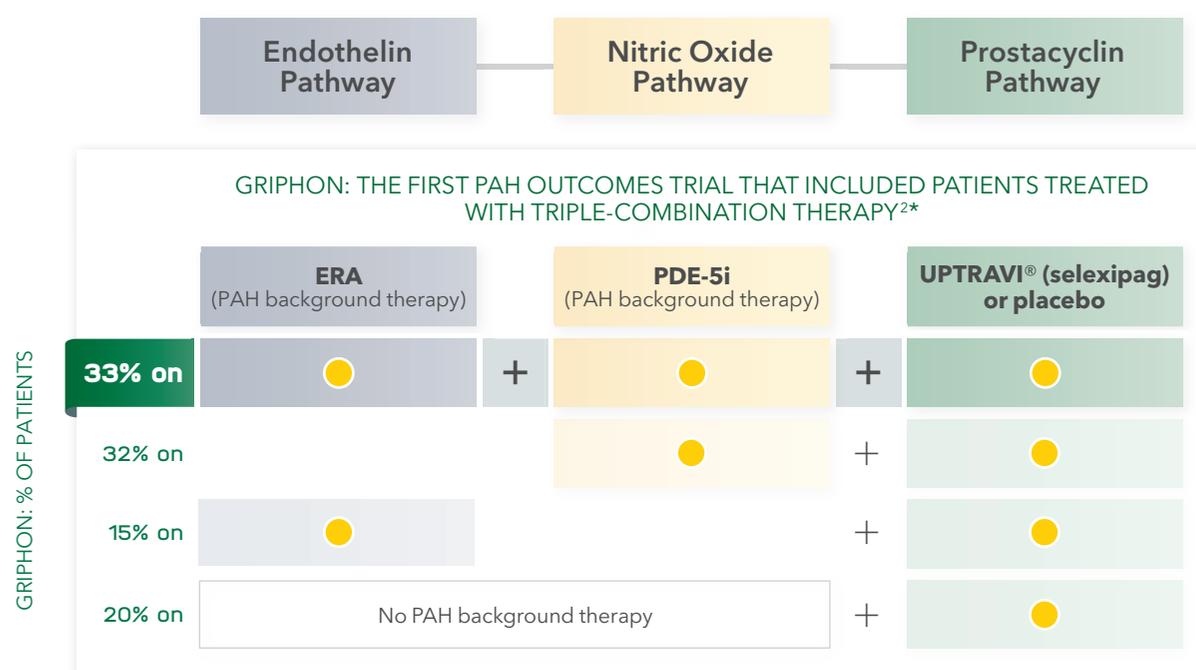
catheter capable of measuring continuous central venous oxygen saturation (ScvO<sub>2</sub>). Patients received crystalloid or colloid until a predetermined central venous pressure was obtained, and if their mean arterial pressure was

still below 65 mm Hg, therapy with pressors was initiated. If their ScvO<sub>2</sub> was not 70% or greater, patients were transfused until their hematocrit was greater than 30%, and, if this still did not bring their ScvO<sub>2</sub> up, patients

were started on a regimen of dobutamine. Multiple trials of varying design subsequently demonstrated efficacy in this approach, which was rapidly adopted worldwide in many centers managing patients with sepsis.

## IN PAH (WHO GROUP I), 3 Key Pathways Are Targeted for Treatment<sup>1</sup>

**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)<sup>3</sup>

### 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 (≥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.

However, many questions remained. All patients were managed the same in EGDT, with no capacity to individualize care, regardless of clinical situation (comorbidities, age, origin of sepsis). In addition, it was never clear which specific elements of the EGDT protocol were responsible for its success, as a bundled protocol could potentially si-

multaneously include beneficial, harmful, and neutral components. Further, many of the elements of EGDT have not been demonstrated to be beneficial in isolation. For example, multiple studies demonstrate that patients not receiving transfusions until their hemoglobin value reaches 7 g/dL is at least as effective as receiving transfusions to

a hemoglobin value of 10 g/dL. Also, there is a wealth of data suggesting that central venous pressure is not an accurate surrogate for intravascular volume.

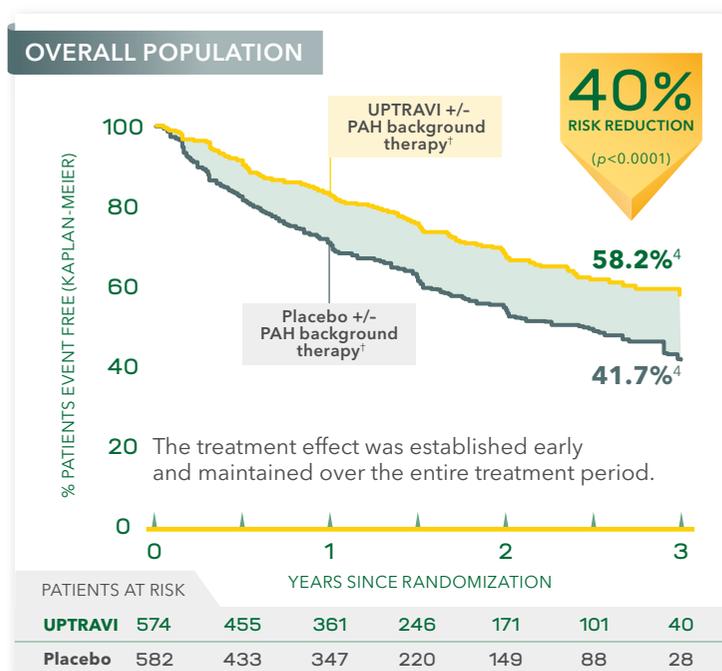
To address these issues, three international, multicentered randomized controlled trials were published in the *New England Journal of Medicine*

in 2014 and 2015: ARISE, ProCESS, and ProMISE (ARISE investigators. *N Engl J Med.* 2014;371[16]:1496; ProCESS investigators. *N Engl J Med.* 2014;370[18]:1683; Mouncey, et al. *N Engl J Med.* 2015;372[14]:1301). Each of these studies randomized patients either to EGDT as defined in the orig-

*Continued on following page*

## Consistent Treatment Effect on Time to First Disease Progression Event, Irrespective of PAH Background Therapy<sup>2</sup>

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%)<sup>‡</sup>
- 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<sup>‡</sup> 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.

<sup>†</sup>An ERA, PDE-5i, or both.

<sup>‡</sup>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](http://www.UPTRAVI.com/hcp) to learn more

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



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Continued from previous page

inal Rivers study or to a “usual care” group with management directed under the guidance of a bedside health-care provider. Across all three trials, the EGDT group received more fluids, inotropes, vasopressors, and transfusions than the “usual care” group.

However, there was no mortality benefit detected in any of the trials.

The difference between the original Rivers trial (demonstrating a huge benefit of EGDT) and the three subsequent trials leads (showing no benefit) was striking and leads to the obvious questions of (a) why were the results so disparate and (b) what should we

do for our patients moving forward? Perhaps the most obvious difference in the trials is the baseline mortality in the “usual care” groups between the studies. In the original Rivers study, in-hospital mortality was 46.5% for the “usual care” group. For ARISE, ProCESS, and ProMISE, 60- to 90-day mortality ranged from 18.8% to 29.2%

in the “usual care” group. This means either that the patients in the original EGDT trial were significantly sicker or that something fundamental has changed over time. A closer review of the papers reveals it is likely the latter as, in actuality, the “usual care” group in the three NEJM trials looked a lot like the EGDT group in the original trial. Most patients received significant volume resuscitation in these studies prior to enrollment, and the original ScvO<sub>2</sub> was 71% in ProCESS (as opposed to 49% in the original Rivers trial). This suggested that increasing awareness of sepsis that occurred during the 15 years between the EGDT trial and the subsequent three trials – likely due to the Surviving Sepsis Campaign, as well as other efforts from both advocacy groups as well as medical organizations – led to better sepsis care on patient presentation. In essence, what was “usual care” in the time of the original EGDT study had become inappropriate care in the modern era, and much of what was protocolized in EGDT had been transformed into “usual care,” even if a specific protocol was not being used. In the setting in which “usual care” had dramatically improved, the original EGDT protocol was not helpful if implemented on all comers. One key reason is that many patients simply improved with volume and antibiotics (which had become “usual care”) and did not need additional interventions. Another reason is that some of the interventions in EGDT (blood transfusion, continuous ScvO<sub>2</sub> monitoring) are likely not beneficial in the majority of cases.

These studies have led to significant changes in recommendations in sepsis management guidelines. The 2016 Surviving Sepsis Campaign guidelines – published after ARISE, ProCESS and ProMISE trials – still recommend antibiotics, cultures, adequate volume resuscitation (without specifying how to do so), targeting an initial mean arterial pressure of 65 mm Hg, and vasopressors if a patient remains hypotensive despite adequate fluids (Rhodes et al. *Crit Care Med.* 2017; 45). However, no recommendations are made regarding mandatory placement of a central venous catheter, measuring central venous pressure, transfusing to higher hemoglobin, etc.

In many ways, the last 15 years of fluid resuscitation in sepsis represents the triumph of evidence-based medicine over opinion-based medicine and the challenges of moving toward precision medicine. When “usual care” was highly variable without a consistent scientific rationale, EGDT markedly improved outcomes – a clear victory of evidence-based medicine that



tablets | 200/600 mcg

#### 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 ≥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 m<sup>2</sup>.

There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates <15 mL/min/1.73 m<sup>2</sup> [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<sub>max</sub> 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 m<sup>2</sup> and < 30 mL/min/1.73 m<sup>2</sup>) [see *Use in Specific Populations*].

##### Drug Interaction Studies:

##### In vitro studies

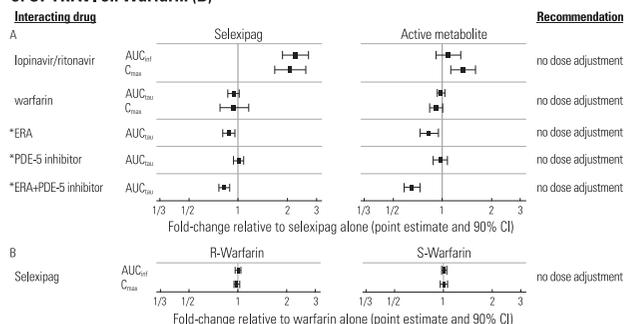
Selexipag is hydrolyzed to its active metabolite by hepatic carboxylesterase 1. Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates 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



likely saved thousands of lives. However, when EGDT effectively became “usual care,” each individual element of EGDT bundled together failed to further improve outcome. The new evidence suggested that for all comers, EGDT is no better than the new normal, and, thus, newer guidelines do not recommend most of its components.

Moving forward, what is the best way to resuscitate newly identified patients with sepsis? A big fear in eliminating EGDT in its entirety is that practitioners will not have any guidance on how to manage resuscitation in sepsis and so will revert to less rigorous practice patterns. While we acknowledge that concern, we are optimistic that the future will continue to yield decreases in sepsis mortality. Optimally, volume status will be assessed on an individual basis. Rather than resuscitating every patient with a one-size-fits-all parameter that is fairly crude at best and inaccurate at worst (central venous pressure), bedside caregivers should use whatever tools are most appropriate to their individual patient and expertise. This could include bedside ultrasound, stroke volume variation, esophageal Doppler, passive leg raise, etc, depending on the clinical situation. The concept of appropriate volume resuscitation raised in EGDT continues to be 100% valid, but the implementation is now patient-specific and will vary upon available technology, provider skill, and bedside factors that might make one method superior to the other. Similarly, the failure of EGDT to improve survival in the ARISE, ProCESS, and ProMISE trials does not mean there is never a role for checking venous blood gases and measuring ScvO<sub>2</sub>. From our point of view, this would be a gross misinterpretation of the trials, as the finding that all elements of EGDT combined fail to benefit all patients with sepsis on arrival should assuredly not be interpreted as none of the elements of EGDT can ever be beneficial in any patients with sepsis. While we can – and should – learn from the data as they pertain

to “all comers,” we equally can – and should – look at each individual patient and determine where they align with what is known (and unknown) in the literature and simultaneously attempt to both personalize and optimize their care utilizing our general knowledge of physiology and individual information that is unique to the patient.

In the future, we hope that sepsis resuscitation will be performed in an analogous fashion to cancer therapy. Understanding a patient’s response at the organ level and cellular and subcellular levels will allow us to individualize initial therapy. For instance, an “omics” evaluation of a patient’s immune system may be helpful for guiding treatment. Distinct patterns of gene and protein expression could potentially demonstrate in advance how different patients will respond differently to the same therapy and, in a dynamic manner, determine whether they are responding according to the expected trajectory. Unfortunately, since this is impractical today, the best we can do is to follow recommendations that are applicable to large populations (the Surviving Sepsis bundles) while simultaneously individualizing therapy when no clear data are available. Further, it is critical to assess and reassess the response at the bedside to optimize outcomes. While it is frustrating that no clear guidance can be given on the best way to measure volume status or fluid responsiveness or when there is utility in measuring ScvO<sub>2</sub>, there is comfort in knowing that best practice has evolved over the past 15 years such that the majority of EGDT is now “usual care.” Moving forward, the challenges in transitioning sepsis resuscitation from population-based evidence-based medicine to individualized therapy are real, but the opportunities for improved outcomes in this deadly disease are enormous.

*Dr. Head is with the Department of Anesthesiology, and Dr. Coopersmith is with the Department of Surgery, Emory Critical Care Center, Emory University School of Medicine, Atlanta, GA.*

## In Memoriam

**S**andra K. Willsie, DO, FCCP, died on March 26, 2017, after a courageous battle with brain cancer. As an osteopathic physician with board certification in internal medicine, pulmonary diseases, and critical care medicine, Sandra worked diligently for over 30 years to further scientific discovery and health-care education.

An NIH-funded career academic awardee, a Macy Institute scholar, and an invited faculty member on health-care leadership at Harvard University, Sandra was very involved in academic medicine. She served as professor of medicine, interim chair of medicine and docent at the University of Missouri–Kansas City School of Medicine; and as provost, dean, vice-dean, and department chair at Kansas City University of Osteopathic Medicine. Sandra earned a master’s degree in bioethics and health policy focusing on research ethics from Loyola University of Chicago Stritch School of Medicine. She made countless scholarly presentations and published regularly.

Sandra made eight pro bono trips to provide physicians in Honduras,

Panama, Costa Rica, and the Dominican Republic the latest research updates on asthma and COPD research. She was honored to serve as president of Women Executives in Science and Healthcare and as board president of the American Heart Association’s Midwest Affiliate. She had been volunteering for over 30 years at the KC CARE Clinic in downtown Kansas City, Missouri, and was a committee member of the FDA advisory panel on respiratory and anesthesiology devices.

Sandra devoted many years of active participation to the American College of Chest Physicians and will be missed by so many colleagues and friends. She served on the Board of Regents and on the US and Canadian Council of Governors, was a member of numerous committees, including Education, Ethics, Marketing, Nominating, and Chair of the Scientific Presentations and Awards Committee. A staunch supporter of the CHEST Foundation, she was instrumental in its creation and served as a board and committee member. We extend our heartfelt condolences to her husband, Tom, and her family and many friends.

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## EDITOR'S NOTE

**W**e must admit that we are all imperfect beings and, as such, we are all incorrect from time to time. In order to evolve to proverbial ‘higher planes of enlightenment,’ we must accept our cognitive errors – sometimes as individuals and other times as a collective entity. Within this framework of improvement through critical reflection, evidence-based medicine has been born. In this commentary, the authors address an area of smoldering contention and conflicting evidence—the role of EGDT in managing sepsis. If their call for an individualized approach to therapy is ultimately the ideal strategy, it may vindicate us all by simultaneously proving us all wrong.

*Lee E. Morrow, MD, FCCP*

# PULMONARY PERSPECTIVES: Ensuring quality for EBUS bronchoscopy with varying levels of practitioner experience

BY AMIT K. MAHAJAN, MD, FCCP; SANDEEP J. KHANDHAR, MD; AND ERIK FOLCH, MD, MSC

ness of EBUS-TBNA improves with increasing number of procedures performed, allowing for access to a greater number of lymph nodes with-

out necessarily increasing the length of the procedure, and by reducing the number of punctures at each nodal station. Based on their results, the

first 20 procedures performed yielded a 70% accuracy, 21 to 40 procedures performed resulted in 81.8% accuracy, 41 to 60 procedures performed

**E**ndobronchial ultrasound (EBUS) bronchoscopy is a tool that has transformed the diagnosis and staging of lung cancer. Through real-time ultrasound imaging, EBUS provides clear images of lymph nodes and proximal lung masses that can be adequately sampled through transbronchial needle aspiration. EBUS is a minimally invasive, outpatient procedure that can also be used for diagnosing benign disease within the chest. Large studies investigating the use of EBUS for mediastinal staging have shown the procedure to be highly sensitive and specific while harboring an excellent safety profile.<sup>1</sup> As a result, EBUS has essentially replaced mediastinoscopy for the staging of lung cancer.

EBUS bronchoscopy was primarily offered at major academic centers when first released and was performed by physicians who were formally trained in the procedure during interventional pulmonology or thoracic surgery fellowships. Over time, the tool has been adopted by established general pulmonologists without formal training in EBUS. Some of these pulmonologists only develop their skills by attending 1- to 2-day courses, which is insufficient supervision to become competent in this important procedure.

An ongoing debate continues as to how many supervised EBUS bronchoscopies should be performed prior to being considered proficient.<sup>2</sup> As procedural competence has been associated with the number of EBUS procedures performed, the learning curve required to master EBUS is an important component of proficiency. While most consider learning curves to be variable, evidence produced by Fernandez-Villar and colleagues revealed that EBUS performance continues to improve up to 120 procedures.<sup>3</sup> This analysis was performed in unselected consecutive patients based on diagnostic yield, procedure length, number of lymph nodes passes performed in order to obtain adequate samples, and the number of lymph nodes studied per patient. The learning curve was evaluated based on consecutive groups of 20 patients, the number of adequate samples obtained, and the diagnostic accuracy. Their results indicated that the diagnostic effective-



FOR UNCONTROLLED ASTHMA IN PATIENTS AGED ≥12 YEARS ON ICS OR ICS+LABA

## SPIRIVA RESPIMAT—A DIFFERENT APPROACH ADDS NEW EXPECTATIONS FOR ASTHMA

SPIRIVA RESPIMAT, 1.25 mcg, is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. SPIRIVA RESPIMAT is not indicated for relief of acute bronchospasm.

### IMPORTANT SAFETY INFORMATION

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

SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an attack, a rapid-acting beta<sub>2</sub>-agonist should be used.

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

Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated with an inhaled short-acting beta<sub>2</sub>-agonist, such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered.



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Printed in U.S.A. (03/16) PC-SVRA-0188-PROF

resulted in 83.3% accuracy, 61 to 80 procedures performed resulted in 89.8% accuracy, 81 to 100 procedures performed resulted in 90.5% accuracy, and 101 to 120 procedures performed resulted in 94.5% accuracy.

While the American Thoracic Society (ATS) and the American College of Chest Physicians (CHEST) both

recommend a minimum number of 40 to 50 supervised EBUS bronchoscopies prior to performing the procedure independently, along with 20 procedures per year for maintenance of competency, most institutions do not track the number of EBUS procedures performed and they do not follow the ATS or CHEST recommen-

dations.<sup>4,5</sup> As a result, a number of physicians are independently performing EBUS without adequate experience, resulting in possibly poor quality care. Unfortunately, some short courses, intended to generate interest and encourage attendees to pursue further training, are mistakenly assumed to be sufficient by the novice user.

As the number of interventional pulmonary fellowships continues to expand, the growing number of subspecialized pulmonologists with extensive training in EBUS grows. During a dedicated interventional pulmonary fellowship, fellows perform well above the number of

*Continued on following page*

SPIRIVA RESPIMAT for ASTHMA | 1.25 mcg/actuation

## An add-on treatment for asthma with proven efficacy and a demonstrated safety profile<sup>1</sup>



Improves lung function\* in asthma patients on ICS and ICS + LABA<sup>1</sup>



Reduces the risk of exacerbations in adult patients<sup>1†</sup>



Delivers a steroid-free, slow-moving mist<sup>1</sup>

\*For peak forced expiratory volume in one second (FEV<sub>1,0-3hr</sub>) and trough FEV<sub>1</sub>.

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

ICS=inhaled corticosteroids; LABA=long-acting beta<sub>2</sub>-agonist.

Treat asthma differently<sup>1</sup>—learn more at [AddOnForAsthma.com](http://AddOnForAsthma.com)



### IMPORTANT SAFETY INFORMATION (continued)

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

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

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

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

The most common adverse reactions >2% incidence and higher than placebo with SPIRIVA RESPIMAT (placebo) in asthma trials in adults were pharyngitis 15.9% (12.4%), sinusitis 2.7% (1.4%), bronchitis 3.3% (1.4%), and headache 3.8% (2.7%).

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

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

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

Reference: 1. SPIRIVA RESPIMAT [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016.

 **SPIRIVA<sup>®</sup> RESPIMAT<sup>®</sup>**  
(tiotropium bromide) INHALATION SPRAY

Continued from previous page

EBUS bronchoscopies suggested by the ATS and CHEST in a single year. Recently published accreditation guidelines require a minimum of 100 cases per interventional pulmonary fellow.<sup>6</sup> These fellowship-trained interventional pulmonologists are then tested to be-

come board-certified in a wide array of minimally invasive procedures, including EBUS. As a result, a model has developed where both board-certified interventional pulmonologists with extensive training in EBUS and general pulmonologists not meeting ATS or CHEST minimum requirements practice at the same institution.

Proponents of a more liberal access to credentialing in EBUS have suggested that adhering to competency requirements constitutes a “barrier to entry” in which incumbent practitioners benefit from limiting competition. However, like any other regulatory metric, the rationale is to prevent asymmetric

information. In this example, the physician knows more than the patient. The patient cannot make an informed decision on which provider to choose and what are the minimum requirements that are likely to produce the most useful information (ie, complete staging). For these reasons, it is imperative

**SPIRIVA® Respimat® (tiotropium bromide) inhalation spray**

**FOR ORAL INHALATION**

Rx only

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

Please see package insert for full Prescribing Information.

**INDICATIONS AND USAGE: Maintenance Treatment of Chronic Obstructive Pulmonary Disease:** SPIRIVA RESPIMAT (tiotropium bromide) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA RESPIMAT is indicated to reduce exacerbations in COPD patients. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm. **Maintenance Treatment of Asthma:** SPIRIVA RESPIMAT is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm.

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

**WARNINGS AND PRECAUTIONS: Not for Acute Use:** SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for COPD and asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an acute attack, a rapid-acting beta<sub>2</sub>-agonist should be used. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, therapy with SPIRIVA RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT. **Paradoxical Bronchospasm:** Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta<sub>2</sub>-agonist such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered. **Worsening of Narrow-Angle Glaucoma:** SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

**ADVERSE REACTIONS:** The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see Warnings and Precautions]; Paradoxical bronchospasm [see Warnings and Precautions]; Worsening of narrow-angle glaucoma [see Warnings and Precautions]; Worsening of urinary retention [see Warnings and Precautions]. Because clinical trials are conducted under

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

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

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

\*Adverse reactions include a grouping of similar terms

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

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

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

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

\*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT 2.5 mcg group at an incidence of 1% to 2% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo included: *Nervous system disorders:* dizziness; *Gastrointestinal disorders:* oropharyngeal candidiasis, diarrhea; *Respiratory system disorders (Upper):* cough, rhinitis allergic; *Renal and urinary disorders:* urinary tract infection; *General disorders and administration site conditions:* pyrexia; and *Vascular disorders:* hypertension. *Less Common Adverse Reactions:* Among the adverse reactions observed in the clinical trials with an incidence of 0.5% to <1% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo were: palpitations, dysphonia, acute tonsillitis, tonsillitis, rhinitis, herpes zoster, gastroesophageal reflux disease, oropharyngeal discomfort, abdominal pain upper, insomnia, hypersensitivity (including immediate reactions), angioedema, dehydration, arthralgia, muscle spasms, pain in extremity, chest pain, hepatic function abnormal, liver function test abnormal. *Adolescent Patients Aged 12 to 17 years:* SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in adolescent patients with asthma. The safety data described below are based on one 1-year and one 12-week double-blind, placebo-controlled trials in a total of 789 adolescent asthma patients on background treatment of at least ICS or ICS plus one or more controller. Of these patients, 252 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 63.9% were male and 95.6% were Caucasian with a mean age of 14.3 years and a mean post-bronchodilator percent predicted FEV<sub>1</sub> of 98.3% at baseline. The adverse reaction profile for adolescent patients with asthma was comparable to that observed in adult patients with asthma. SPIRIVA RESPIMAT 5 mcg also has been compared to placebo in seven placebo-controlled parallel-group trials ranging from 12 to 52 weeks of treatment duration in

that regulations protect the patient.

Without question, EBUS bronchoscopy should not be performed only by board-certified interventional pulmonologists. Instead, hospital credentialing committees should adhere to both the ATS and CHEST recommendations for the number of supervised cases necessary prior to

## Proponents of a more liberal access to credentialing in EBUS have suggested that adhering to competency requirements constitutes a “barrier to entry” in which incumbent practitioners benefit from limiting competition.

performing EBUS independently. As EBUS use continues to grow, fellows in 3- or 4-year pulmonary and critical

care fellowships will be likely capable of meeting the minimal number of observed cases, but, if these numbers

are not achieved, additional training should be required. Understandably, this could be challenging for physicians who are unable to take time away from their practice to gain this training. However, if these numbers cannot be met, credentialing requirements should be enforced.

Even more challenging than establishing quality measures for EBUS, is to ensure the highest level of care delivery for patients when there exist multiple levels of experience in the same institution. Undoubtedly, patients undergoing EBUS bronchoscopy, or any procedure for that matter, would want the most skilled physician who has attained certification in the procedure. Unfortunately, no formal certification of EBUS exists outside of gaining board certification in interventional pulmonology. To ensure excellence in care, physicians performing EBUS should be involved in quality improvement initiatives and review pathologic yields along with complications on a regular basis in a group setting. Unlike emergency interventions, EBUS bronchoscopy is an entirely elective procedure.

The advent of EBUS bronchoscopy has revolutionized the diagnosis and staging of lung cancer. As use of EBUS continues to become more widespread, the incidence of high volume and low volume proceduralists will become a more commonly encountered scenario. Guidelines have been set by the professional pulmonary societies based on the data and observations available. At the local level, stringent guidelines need to be established by hospitals to ensure a high level of quality with appropriate oversight. Patients undergoing EBUS deserve a physician who is skilled in the procedure and has performed at least the minimum number of procedures to provide the adequate care.

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4149 adult patients (aged 18 to 75 years) with asthma and in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in 789 adolescent patients (1370 adults and 264 adolescents receiving SPIRIVA RESPIMAT 5 mcg once-daily). The adverse reaction profile for SPIRIVA RESPIMAT 5 mcg in patients with asthma was comparable to that observed with SPIRIVA RESPIMAT 2.5 mcg in patients with asthma. **Postmarketing Experience:** In addition to the adverse reactions observed during the SPIRIVA RESPIMAT clinical trials in COPD, the following adverse reactions have been identified during the worldwide use of SPIRIVA RESPIMAT 5 mcg and another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder): glaucoma, intraocular pressure increased, vision blurred, atrial fibrillation, tachycardia, supraventricular tachycardia, bronchospasm, glossitis, stomatitis, dehydration, insomnia, hypersensitivity (including immediate reactions), and urticaria.

**DRUG INTERACTIONS: Concomitant Respiratory Medications:** SPIRIVA RESPIMAT has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, and anti-IgE treatment without increases in adverse reactions. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions and Adverse Reactions].

**USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects:** Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential

risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m<sup>2</sup> basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 40 times the MRHDID (on a mcg/m<sup>2</sup> basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 430 times the MRHDID (on a mcg/m<sup>2</sup> basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m<sup>2</sup> basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). **Labor and Delivery:** The safety and effectiveness of SPIRIVA RESPIMAT has not been studied during labor and delivery. **Nursing Mothers:** Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA RESPIMAT is administered to a nursing woman. **Pediatric Use:** The safety and efficacy of SPIRIVA RESPIMAT 2.5 mcg have been established in adolescents (aged 12 to 17 years) with asthma in 3 clinical trials up to 1 year in duration. In the 3 clinical trials, 327 patients aged 12 to 17 years with asthma were treated with SPIRIVA RESPIMAT 2.5 mcg. Patients in this age group demonstrated efficacy results similar to those observed in patients aged 18 years and older with asthma. The adverse drug reactions profile for this age group was comparable to that observed for patients aged 18 years and older with asthma. Based on available data, no adjustment of dosage of SPIRIVA RESPIMAT in

adolescent patients with asthma is warranted. The safety and efficacy of SPIRIVA RESPIMAT have not been established in pediatric patients less than 12 years of age. **Geriatric Use:** Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted. Thirty nine percent of SPIRIVA RESPIMAT clinical trial patients with COPD were between 65 and 75 years of age and 14% were greater than or equal to 75 years of age. Approximately seven percent of SPIRIVA RESPIMAT clinical trial patients with asthma were greater than or equal to 65 years of age. The adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Renal Impairment:** Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [see Warnings and Precautions]. **Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. **OVERDOSAGE:** High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. Treatment of overdosage consists of discontinuation of SPIRIVA RESPIMAT together with institution of appropriate symptomatic and/or supportive therapy.

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### EDITOR'S NOTE

**D**r. Mahajan and colleagues present a compelling case for requiring minimum standards to perform an EBUS-guided bronchoscopy. Their opinion piece epitomizes the classic tension between physicians with advanced training and those who can only have practice-based training. A middle ground may exist, as perhaps competence could be achieved by simulation, clinical cases performed, and observation by a regional expert? Physicians in practice must have a pathway to adopt new technology whether it is thoracic ultrasound or endobronchial ultrasound, but it must be done in a safe manner. As a referring physician, I would only send my patients who required mediastinal staging to a pulmonologist who I knew performed EBUS regularly.

Nitin Puri, MD, FCCP

## This month in *CHEST*: Editor's picks

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

### ORIGINAL RESEARCH

Clinical Predictors of Hospital Mortality Differ Between Direct and Indirect ARDS. By Dr. L. Luo, et al.

Cross-Disciplinary Analysis of Lymph Node Classification in Lung Cancer on CT Scanning. By Dr. A. H. El-Sherief, et al. (Podcast)

### GIANTS IN CHEST MEDICINE

Professor James C. Hogg. By Dr. Manuel G. Cosio.

### COMMENTARY

Pulmonary Hypertension Care Center Network: Improving Care and Outcomes in Pulmonary Hypertension. By Dr. S. Sahay, et al.

### EVIDENCE-BASED MEDICINE

Use of Management Pathways or Algorithms in Children With Chronic Cough: CHEST Guideline and Expert Panel Report. By Dr. A. B.



Chang, et al; on behalf of the CHEST Expert Cough Panel.

Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report. By Dr. A. Molassiotis, et al; on behalf of the CHEST Expert Cough Panel.

Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. By Dr. A. B. Chang, et al; on behalf of the CHEST Expert Cough Panel.



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**Bronchoscopy and Pleural  
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Critical Care Medicine Fellows**  
July 21

**Mechanical Ventilation: Advanced  
Critical Care Management**  
July 28-30

**Comprehensive Pleural  
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August 4-5

**Critical Skills for Critical Care:  
A State-of-the-Art Update and  
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August 11-13

**Ultrasonography: Essentials  
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**Cardiopulmonary Exercise  
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**Comprehensive Bronchoscopy  
With Endobronchial Ultrasound**  
September 29 - October 1

**Critical Care Ultrasound:  
Integration into Clinical  
Practice**  
November 10-12

# NETWORKS: Uranium mining, hyperoxia, palliative care education, OSA impact

## Occupational and Environmental Health

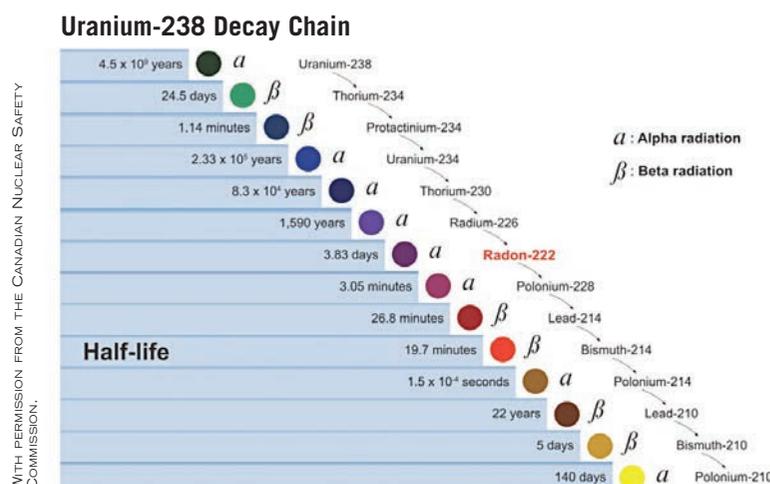
### Health effects of uranium mining Decay series of U 238

Prior to 1900, uranium was used only for coloring glass. After discovery of radium by Madame Curie in 1898, uranium was widely mined to obtain radium (a decay product of uranium).

While uranium was not directly mined until 1900, uranium contaminants were in the ore in silver and cobalt mines in Czechoslovakia, which were heavily mined in the 18th and 19th centuries.

Increased mortality was described in these miners in 1770. In 1878, Harting and Hesse (a public health officer and a local mine physician) described 23% mortality from lung cancer in 650 Schneeberg cobalt miners over 10 years. By the 1920s, 50% of exposed miners were dying of lung cancer.

There were no reports (written in English) of lung cancer associated with



radiation until 1942; but in 1944, these results were called into question in a monograph from the National Cancer Institute. The carcinogenicity of radon was confirmed in 1951; however, this remained an internal government document until 1980. By 1967, the increased prevalence of lung cancer in uranium miners was widely known. By 1970, new ventilation standards for uranium mines were established.

Lung cancer risk associated with uranium mining is the result of exposure to radon gas and specifically

radon progeny of Polonium 218 and 210. These radon progeny remain suspended in air, attached to ambient particles (diesel exhaust, silica) and are then inhaled into the lung, where they tend to precipitate on the major airways. Polonium 218 and 210 are alpha emitters, which have a 20-fold increase in energy compared with gamma rays (the primary radiation source in radiation therapy). Given the mass of alpha particles (two protons and two neutrons), they interact with superficial tissues; thus, once deposited in the

large airways, a large radiation dose is directed to the respiratory epithelium of these airways.

Occupational control of exposure to radon and radon progeny is accomplished primarily by ventilation. In high-grade deposits of uranium, such as the 20% ore grades in the Athabasca Basin of Saskatchewan, remote control mining is performed.

Smoking, in combination with occupational exposure to radon progeny, carries a greater than additive but less than multiplicative risk of lung cancer.

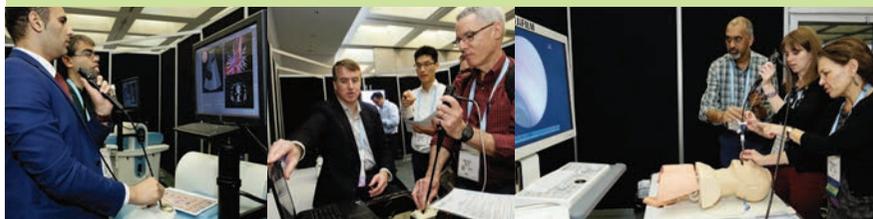
In addition to the lung cancer risk associated with radon progeny exposure, uranium miners share the occupational risks of other miners: exposure to silica and diesel exhaust. Miners are also at risk for traumatic injuries, including electrocution.

Health effects associated with uranium milling, enrichment, and tailings will be discussed in a subsequent *CHEST Physician* article.

Richard B. Evans, MD, MPH, FCCP  
Steering Committee Chair

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### Bronchoscopy Procedures for the ICU May 6-7

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Key topics: Massive hemoptysis, bronchoscopy-guided percutaneous tracheostomy, foreign body extraction, and bronchoscopy for patients with difficult airways or critically ill patients requiring diagnostic bronchoscopy supported by noninvasive positive pressure ventilation (NIPPV)

### 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

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## Respiratory Care

### Hyperoxia in critically ill

#### patients: What's the verdict?

Oxygen saturation is considered to be the “fifth vital sign,” and current guidelines recommend target oxygen saturation (SpO<sub>2</sub>) between

94% and 98%, with lower targets for patients at risk for hypercapnic respiratory failure (O’Driscoll BR et al. *Thorax*. 2008;63(suppl):vi1). Oxygen toxicity is well-demonstrated in

experimental animal studies. While its incidence and impact on outcomes is difficult to determine in the clinical setting, increases in-hospital mortality have been associated with hyperoxia in patients with cardiac arrest, acute myocardial infarction, and stroke (Kligannon et al. *JAMA*. 2010;303[21]:2165; Stub et al. *Circulation*. 2015;131[24]:2143; Rincon et al. *Crit Care Med*. 2014;42[2]:387).

Girardis and colleagues examined the impact of conservative oxygen administration (PaO<sub>2</sub> maintained between 70-100 mm Hg or SpO<sub>2</sub> between 94-98%) vs standard care group (permitting PaO<sub>2</sub> values up to 150 mm Hg or SpO<sub>2</sub> values between 97-100%) in ICU patients admitted for at least 72 hours (Girardis et al. *JAMA*. 2016;316[15]:1583). There were striking differences in ICU

mortality between the two groups with absolute risk reduction of 8.6% (P = .01) favoring the conservative oxygen therapy group, as well as significant reductions in episodes of shock, liver failure, and bacteremia. However, there were baseline differences in the severity of illness between the two groups: the use of a modified intention to treat analysis and the early termination of the trial mitigate the robustness of these findings.

Complementing the findings of Girardis and colleagues, a recent analysis of more than 14,000 critically ill patients, found that time spent at PaO<sub>2</sub> > 200 mm Hg was associated with excess mortality and fewer ventilator-free days (Helmerhorst et al. *Crit Care Med*. 2017;45[2]:187).

While other trials demonstrated safety and feasibility of conservative oxygen therapy in critically ill patients (Panwar et al. *Am J Respir Crit Care Med*. 2016;193[1]:43; Helmerhorst et al. *Crit Care Med*. 2016;44[3]:554; Suzuki et al. *Crit Care Med*. 2014;42[6]:1414), they did not find significant differences between conservative and liberal oxygen therapy with regards to new organ dysfunction or mortality. However, the degree of hyperoxia was usually more modest than in either the Girardis trial or the Helmerhorst (2017) analysis.



DR. KAUR



DR. BOWTON

# NETWORKS CHALLENGE

2017 NETWORKS CHALLENGE  
Conquer the Challenge. Champion Lung Health.



2017 NETWORKS CHALLENGE  
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#### ROUND 1 April 18- June 30

##### Who:

NetWork Steering Committee members

##### How to Participate:

Members will compete by donating or pledging any amount to the CHEST Foundation in 2017. In order to count any gifts made from January 1 - April 18, participants must email [chestfoundation@chestnet.org](mailto:chestfoundation@chestnet.org) with their NetWork name, and the date and amount of their gift.

##### Where Your Money Goes:

Proceeds donated in this round will fund our Travel Grants program, bringing young professionals to the CHEST Annual Meeting.

##### How to Win:

Round 1 winners will be determined by the top two NetWork Steering Committees with the highest percentage of participation.

##### What You Win:

The two winning NetWork Steering Committees receive the following:

- Up to two travel grants to CHEST 2017.
- First place—a 75-minute session on Sunday from 10:45 am to 12 pm.
- Second place—a 60-minute session on Monday from 1:30 pm to 2:30 pm.

#### ROUND 2 July- CHEST 2017

##### Who:

NetWork Steering Committee members

##### How to Participate:

Members will compete by donating or pledging any amount to the CHEST Foundation in 2017.

##### Where Your Money Goes:

Proceeds donated in Round 2 will fund two new community service initiatives, which will be chosen and created by the two winning NetWorks.

##### How to Win:

Round 2 winners will be determined by the total amount contributed by the top two NetWorks Steering Committees.

##### What You Win:

The two winning NetWork Steering Committees receive the following:

- Community Service initiative, designed and created by the winning NetWorks. Winning NetWorks must raise a minimum of \$5,000 each in order to fund their own community service initiative. Donations in 2017 will count toward the \$5,000 minimum.
- Up to two travel grants to CHEST 2018.

#### ROUND 3 CHEST 2017

##### Who:

All CHEST NetWork Members

##### How to Participate:

Members will compete by donating or pledging any amount to the CHEST Foundation during CHEST 2017.

##### Where Your Money Goes:

Proceeds donated in Round 3 will fund two new patient education guides. The topics of the guides will be chosen and created by the two winning NetWorks.

##### How to Win:

Round 3 winners will be determined by the highest percentage of participation by the top two NetWorks' membership.

##### What You Win:

The two winning NetWork Steering Committees receive the following:

- The creation of a patient education guide. The topic of each guide created will be determined and developed by each winning NetWork. Winning NetWorks must raise a minimum of \$10,000 each in order to fund their own patient education guide. Donations in 2017 will count toward the \$10,000 minimum.
- Up to two travel grants to CHEST 2018.



To donate today, go to [chestfoundation.org/donate](http://chestfoundation.org/donate).

For more information, contact Chloé Daniels at [cdaniels@chestnet.org](mailto:cdaniels@chestnet.org).

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## Mon General



### Pulmonologist and Critical Care Physician

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The 189-bed not-for-profit community hospital recently completed a \$92M renovation and expansion. Mon General Hospital is one of only 2% of hospitals nationally awarded both a Patient Safety Award and a Patient Experience Award by Healthgrades, a leading online resource for comprehensive information about physicians and hospitals. We are a Level IV Trauma Center and a certified Chest Pain Center with a university hospital operating a Level I trauma center is less than 1 mile away.

Morgantown is a lovely place to practice medicine. Home to West Virginia University, the area has amenities that only a “college town” offers – great sports, theatre, shopping, nightlife and restaurants. Morgantown is a short drive to Pittsburgh, 3-4 hours to the Baltimore/Washington Metro area. Within an hour’s drive you’ll find class 4-5 white water rafting, snow/water skiing, mountain biking, hunting, fishing, golfing and a quality of life that is increasingly difficult to find. It also boasts an excellent public and private school system.

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## PROFESSIONAL OPPORTUNITIES

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### 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.

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Please reply with CV to Human Resources, Minnesota Lung Center / Minnesota Sleep Institute, 920 East 28<sup>th</sup> Street, Suite 700, Minneapolis, Minnesota 55407. Fax: 612-871-4883 or by email to [dh@mlc-msi.com](mailto:dh@mlc-msi.com) [www.minnlung.com](http://www.minnlung.com)

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Based on current evidence, it seems appropriate to maintain physiologically normal levels of PaO<sub>2</sub> without causing hyperoxia in critically ill patients. Oxygen saturation greater than 97% or 98% for prolonged periods should be avoided. Further randomized controlled trials are needed to more clearly elucidate appropriate targets for oxygenation and their impact on patient outcomes.

Amanpreet Kaur, MD

Steering Committee Fellow-in-Training

David L. Bowton, MD, FCCP

Steering Committee Chair

## Palliative and End-of-Life Care

### Education in palliative medicine

Prompted by concerns that the Affordable Care Act would be instituting “death panels” as part of cost-containment measures, “Dying in America” (a 2015 report of the Institute of Medicine [IOM]) identified compassionate, affordable, and effective care



DR. JOHNSON

for patients at the end of their lives as a “national priority” in American health care. The IOM identified the education of all primary care providers in the delivery of basic palliative care, specifically commenting that all clinicians who manage patients with serious, life-threatening illnesses should be “competent in basic palliative care” (IOM, The National Academies Press 2015).

Considerable effort has been put into providing clinicians with tools to gain this competence. Resources exist from organizations, ranging from the American Academy of Hospice and Palliative Medicine to the American College of Surgeons. Numerous publications address everything from symptom management to teaching communication skills to medical students and residents. But the question remains – can physicians who have been trained to “tread with care in matters of life and death” balance comfort with cure (Lasagna 1964, Modern Hippocratic Oath)? We believe the answer ultimately is yes, and that this balance may prove to be the antidote to the pervasive issues of burnout that plague our profession.

Check out our NetWork Storify page later this year for links to the ongoing discussion surrounding palliative care in medicine and for useful tools in the effort to provide palliative care to all our patients.

Laura Johnson, MD, FCCP  
Steering Committee Vice Chair

## Sleep Medicine

### The impact of sleep apnea: Why should we care?

With recent large trials such as the SAVE and the SERVE-HF studies challenging the cardiovascular benefits of treating sleep-disordered breathing in specific patient subsets, many physicians may start to question, “Why all the fuss?” The Sleep NetWork is bringing the leaders in the field to CHEST 2017 to discuss their take on where we stand with the connection between sleep-disordered breathing and cardiovascular disease, so stay tuned!

Meanwhile, we might reflect on the safety, social, and economic impacts of OSA and its treatment. Sleepiness due to OSA significantly affects driving performance and has received significant attention from the Federal Motor Carrier Safety Administration (FMCSA). Patients with OSA are six times more likely to have a motor vehicle crash than those without OSA (Terán-Santos et al. *N Engl J Med.* 1999;340[11]:847). One transportation company, Schneider, has incorporated an OSA screening and treatment program and reported



DR. DAS

a 73% reduction in preventable driving accidents.

Our relationships, general health, and work productivity can be affected by untreated OSA. The effect on daily life may not be initially obvious. Patients often present only at the insistence of their partner or physician, only to be surprised at how much better they feel once treated. Symptoms of OSA are associated with a higher rate of impaired work performance, sick leave, and divorce (Grunstein et al. *Sleep.* 1995;18[8]:635). A recent survey estimates an \$86.9 billion loss of workplace productivity due to sleep apnea in 2015 (Frost & Sullivan. Hidden health crisis costing America billions. AASM; 2016. <http://www.aasmnet.org/Resources/pdf/sleep-apnea-economic-crisis.pdf>. Accessed March 21, 2017.). The same survey found that among those who are employed, treating OSA was associated with a decline in absences by 1.8 days per year and an increase in productivity 17.3% on average. Considering that the majority of OSA remains undiagnosed, this could have tremendous economic impact.

OSA is an important public health burden. The Sleep NetWork is committed to increasing awareness among individuals (patients and clinicians) and institutions (transportation agencies, government) of the impact of sleep-disordered breathing on society.

Aneesa Das, MD, FCCP  
Steering Committee Chair

# Visit some of Toronto's best during CHEST 2017

Get ready to visit the metropolitan hub of Canada. Explore new grounds with the chest medicine community for current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats.

You will have access to our cutting-edge education, Oct 28 - Nov 1, but don't forget to take advantage of all that Toronto has to offer.

### Food

Are you a foodie? Or do you just enjoy a great meal? Breakfast and brunch are the best ways to start off your day, and there's no shortage of spots in the Toronto area to get your fix. No matter what you're craving, there's a place for you.

Le Petit Dejeune offers an ever-changing menu that ranges from less expensive items, like soup, sandwiches, and salads, to some pricier stuffed crepes, quiche, and eggs florentine. While most Sundays, Saving Grace is packed, but there's only a 15-minute wait, and the atmosphere is quite pleasant. Looking for the perfect cinnamon bun? Rosen's Cinnamon Buns is the place to go. But you have to look closely for the bakery's name, since the sign above the window still advertises the hair salon that used to reside in the same spot!

## CHEST<sup>®</sup> Annual Meeting 2017

### Nature parks

One of the city's largest and oldest parks, High Park is Toronto's version of New York City's Central Park. There's plenty to enjoy, such as Grenadier Pond, numerous ravine-based hiking trails, playgrounds, athletic areas, restaurants, a museum, and even a zoo!

If you want a different type of nature excursion, there is always beautiful Niagara Falls, Ontario, which is just a short drive from Toronto. Don't miss seeing the Tesla monument in Queen Victoria Park, or go 10 minutes north of the Falls to the Botanical Gardens, home to the Butterfly Conservatory with over 2,000 butterflies.

### Relaxation

After eventful days of absorbing all the new science CHEST 2017 has to offer, you may want to relax your mind and body. Elmwood spa, located

in downtown Toronto, is where “four spacious floors of treatment and renewal options mean that Elmwood Spa can provide the convenience and flexibility to cater to demanding schedules,” according to Elmwood.

Learn more about Toronto opportunities at [blogTO.com](http://blogTO.com), and find out more about CHEST 2017 at [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org).

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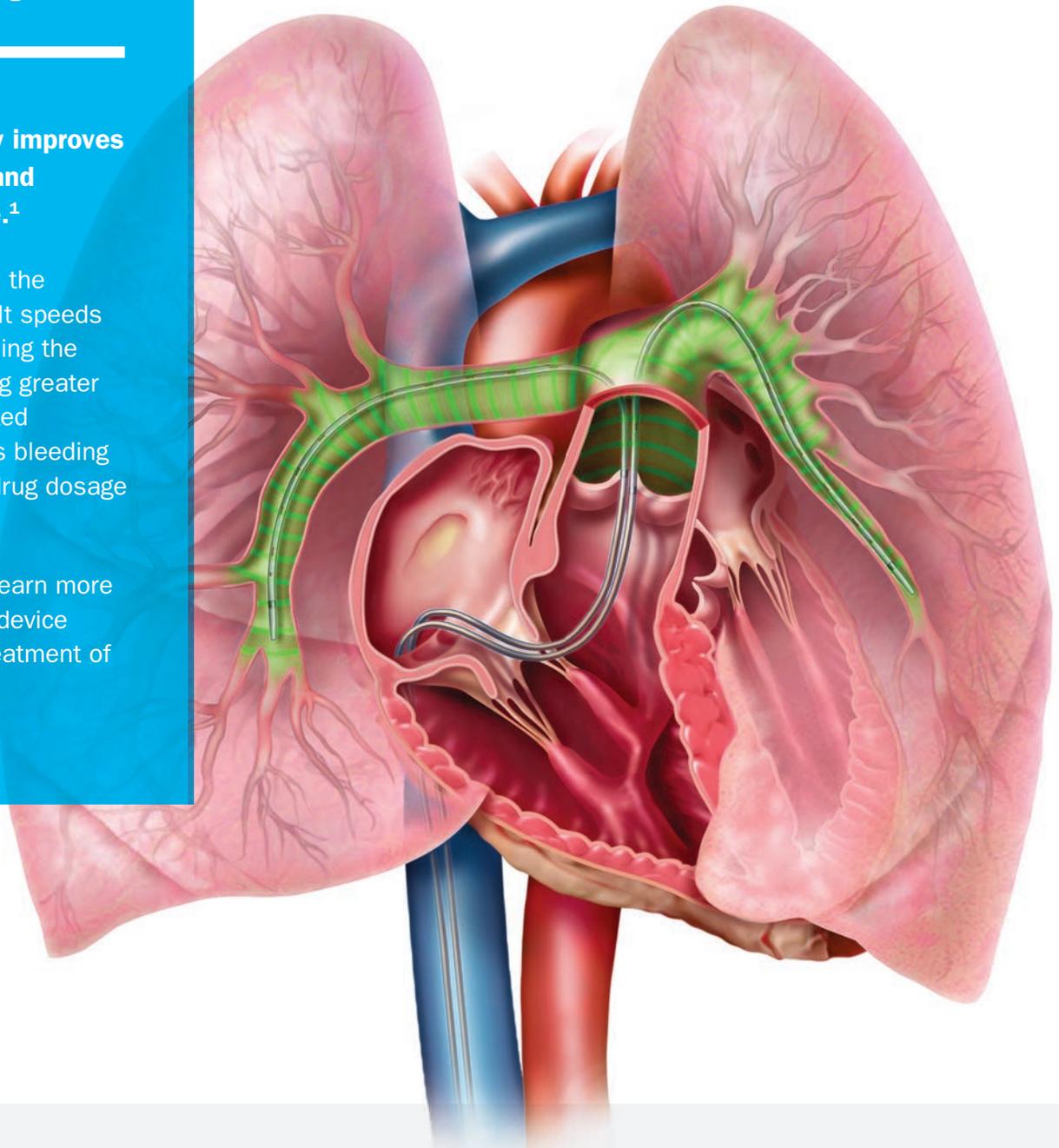
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<sup>3</sup> Kucher, N., et al., *Circulation*, Vol. 129, No. 4, 2014, 479-486.

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

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