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FRONTLINE MEDICAL NEWS

"We are going to have to rewrite the guidelines and change our algorithms," Dr. Jadwiga Wedzicha predicted.

LABA-LAMA bests LABA-steroid in COPD

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – It may be time to revise guidelines for treatment of chronic obstructive pulmonary disease (COPD) complicated by exacerbations, based on data from a phase III trial reported at an international conference of the American Thoracic Society.

The trial, known as FLAME, undertook a head-to-head comparison of two inhaled drug combinations in more than 3,300 patients from 43 countries. Patients were randomized to once-daily indacaterol (a

long-acting beta-agonist, or LABA, bronchodilator) and glycopyrronium (a long-acting muscarinic antagonist, or LAMA, bronchodilator), or to twice-daily salmeterol, also a LABA bronchodilator, and the inhaled glucocorticoid fluticasone.

After a year, the annual rate of COPD exacerbations was 11% lower with indacaterol-glycopyrronium than with salmeterol-fluticasone, according to results reported in a press conference and simultaneously published (*N Engl J Med.* 2016 May 15. doi: 10.1056/NEJMoa1516385).

The difference not only met

See **COPD** • page 7

CPAP protective in mild stroke patients with sleep apnea

Fewer recurrent vascular events.

BY BRUCE JANCIN
Frontline Medical News

DENVER – Long-term continuous positive airway pressure (CPAP) for treatment of sleep apnea in patients with a recent mild stroke or transient ischemic attack resulted in improved cardiovascular and metabolic risk factors, better neurologic function, and a reduction in the recurrent vascular event rate, compared with usual care in the SLEEP TIGHT study.

"Up to 25% of patients will have a stroke, cardiovascular event, or death within 90 days after a minor stroke or TIA [transient

ischemic attack] despite current preventive strategies. And, importantly, patients with a TIA or stroke have a high prevalence of obstructive sleep apnea – on the order of 60%-80%," explained Dr. H. Klar Yaggi at the annual meeting of the Associated Professional Sleep Societies.

SLEEP TIGHT's findings support the hypothesis that diagnosis and treatment of sleep apnea in patients with a recent minor stroke or TIA will address a major unmet need for better methods of reducing the high vascular risk present in this population, said Dr.

See **SLEEP TIGHT** • page 6

Helmet cut intubation rate in ARDS

BY HEIDI SPLETE
Frontline Medical News

Treating acute respiratory distress syndrome patients with helmets instead of face masks reduced intubation and 90-day mortality rates, based on data from a randomized trial of 83 adults published in *JAMA*.

Intubation incidence was

18% in 44 patients treated with helmets, compared with 62% for 39 patients treated with face masks.

In addition, patients in the helmet group had significantly more ventilator-free days than the mask group (28 vs. 13; *P* less than .001), and both hospital mortality and 90-day mortality rates were significantly lower in

the helmet group compared to the mask group (27% vs. 49%; *P* = .04 and 34% vs. 56%; *P* = .02, respectively)

Adverse event rates were rare and similar between the helmet and mask groups. Three interface-related skin ulcers occurred in each group; nose ulcers in 7% of the mask group and neck ul-

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HELP PRESERVE MORE LUNG FUNCTION

Reduce lung function
decline with Esbriet¹⁻⁴



DEMONSTRATED EFFICACY*

- Esbriet had a significant impact on lung function vs placebo in ASCEND^{2,3}
 - 48% relative reduction in risk of a meaningful decline in lung function ($\geq 10\%$ decline in %FVC) at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference; $P < 0.001$)**
 - 2.3x as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference; $P < 0.001$)**
- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND^{2,3}**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006^{2,4}**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)²



ESTABLISHED MANAGEMENT PLAN

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



COMMITTED TO PATIENTS

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



WORLDWIDE PATIENT EXPERIENCE

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

Indication

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

Select Important Safety Information

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

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

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

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

Genentech

A Member of the Roche Group

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

Conditional recommendation, moderate confidence in estimates of effect.^{5†}

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Esbriet[®]
(pirfenidone) capsules 267 mg

Lebrikizumab boosts lung function in asthma

BY BRUCE JANCIN
Frontline Medical News

LOS ANGELES – The investigational interleukin-13 inhibitor lebrikizumab provides a clinically meaningful im-

provement in measures of lung function within 1 week after the first dose in patients with moderate-to-severe uncontrolled asthma on standard-of-care therapy and a high baseline serum periostin level, Dr. Jonathan

Corren reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

He presented a post hoc analysis of three phase II randomized trials of lebrikizumab as add-on therapy in a

total of 558 patients with uncontrolled asthma while on a moderate- or high-dose inhaled corticosteroid plus at least one other controller medication, most often a long-acting beta agonist. The post hoc analysis included 333

Esbriet[®]
(pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

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

5.2 Photosensitivity Reaction or Rash

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

5.3 Gastrointestinal Disorders

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

6 ADVERSE REACTIONS

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

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

ESBRIET[®] (pirfenidone)

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

asthma patients who received lebrikizumab subcutaneously at 125 or 250 mg every 4 weeks for 12 weeks and 225 who got placebo.

Baseline serum periostin levels were 50 ng/mL or higher in 252 participants.

One week after the first dose of lebrikizumab, the high serum

periostin group demonstrated a placebo-subtracted mean 147-mL improvement from baseline in pre-bronchodilator FEV₁.

The week 1 improvement in FEV₁ with lebrikizumab in the low serum periostin group was more modest: a placebo-subtracted 57 mL.

The response to lebrikizumab

was maintained through 12 weeks of once-monthly therapy, with a mean placebo-subtracted week 12 improvement in FEV₁ of 198 mL in the high-periostin group, compared with 74 mL in low-periostin patients. The lebrikizumab-treated group with high baseline periostin had a 16% improvement from baseline in FEV₁

as compared with a 5% improvement in placebo-treated patients with high periostin.

The three trials were known by the acronyms MILLY, LUTE, and VERSE. Dr. Corren was first author of the MILLY study (N Engl J Med. 2011 Sep 22;365(12):1088-98).

MILLY was the initial report that lebrikizumab performed markedly better in patients with uncontrolled asthma and a high baseline serum periostin – a biomarker for IL-13 activity – and that periostin was a better predictor of response to lebrikizumab than either blood eosinophil count or serum IgE, said Dr. Corren of the University of California, Los Angeles.

Lebrikizumab is an IgG4 humanized monoclonal antibody that binds



BRUCE JANCIN/FRONTLINE MEDICAL NEWS

The lebrikizumab-treated group with high baseline periostin had a 16% improvement from baseline in FEV₁, Dr. Corren said.

to IL-13 with high affinity. Its efficacy in the phase II trials confirms the importance of IL-13 as a mediator of disease activity in a subset of asthma patients with activation of Type 2 lymphocytes.

“We know specifically that IL-13 has some very important effects in asthma, including upregulation of adhesion molecules that allow eosinophils to stick in the lung, as well as promoting hyperplasia of smooth muscle and mucus cell hyperplasia with increased mucus secretion.

Immunologically, it allows switching from IgM to IgE on the surface of B cells. So IL-13 is a cytokine that literally makes people atopic,” Dr. Corren explained in an interview.

Several ongoing phase III randomized trials of lebrikizumab in adults with uncontrolled asthma despite standard-of-care therapy are due to be completed in the first half of 2017.

Dr. Corren reported receiving research funding from Roche/Genentech, which sponsored the studies.

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ESBRIET® (pirfenidone)

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

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

Strong CYP1A2 Inhibitors

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

Moderate CYP1A2 Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

7.2 CYP1A2 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal dose of 1000 mg/kg/day).

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

ESBRIET® (pirfenidone)

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see *Dosage and Administration section 2.2 in full Prescribing Information*].

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

8.7 Renal Impairment

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

8.8 Smokers

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

10 OVERDOSAGE

There is limited clinical experience with 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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CPAP reduced vascular events

SLEEP TIGHT from page 1

Yaggi, of Yale University in New Haven, Conn.

SLEEP TIGHT was a National Heart, Lung, and Blood Institute–sponsored phase II, 12-month, multicenter, single-blind, randomized, proof-of-concept study. It included 252 patients, 80% of whom had a recent minor stroke, the rest a TIA. These were patients with high levels of cardiovascular risk factors: two-thirds had hypertension, half were hyperlipidemic, 40% had diabetes, 15% had a prior MI, 10% had atrial fibrillation, and the group's mean body mass index was 30 kg/m².

Polysomnography revealed that 76% of subjects had sleep apnea as defined by an apnea-hypopnea index of at least 5 events per hour. In fact, they averaged about 23 events

per hour, putting them in the moderate-severity range. As is common among stroke/TIA patients with sleep apnea, they experienced less daytime sleepiness than is typical in a sleep clinic population, with a mean baseline Epworth Sleepiness Scale score of 7.

Participants were randomized to one of three groups: a usual care control group, a CPAP arm, or an enhanced CPAP arm. The enhanced intervention protocol was designed to boost CPAP adherence; it included targeted education, a customized cognitive intervention, and additional CPAP support beyond the standard CPAP protocols used in sleep medicine clinics. Patients with sleep apnea in the two intervention arms were then placed on CPAP.

At 1 year of follow-up, the stroke rate was 8.7 per 100 patient-years in the usual care group, compared with 5.5 per 100 person-years in the combined intervention arms. The composite cardiovascular event rate, composed of all-cause mortality,



In the CPAP arms, 58% had a NIH Stroke Scale score of 0-1, compared with 38% of the usual care group.

DR. YAGGI

patients were rated as having good adherence, 30% made some use of the therapy, and 30% had no or poor adherence. Nonetheless, patients in the two intervention arms did significantly better than the usual care group in terms of 1-year changes in insulin resistance and glycosylated hemoglobin. They also had lower 24-hour mean systolic blood pressure and were more likely to convert to a favorable pattern of nocturnal blood pressure dipping. However, no differences between the intervention and usual care groups were seen in levels of high-sensitivity C-reactive protein and interleukin-6.

Fifty-eight percent of patients in the intervention arms ended up with a desirable National Institutes of Health Stroke Scale score of 0-1, compared with 38% of the usual care group. Additionally, daytime sleepiness was reduced at last follow-up to a significantly greater extent in the CPAP groups, Dr. Yaggi noted. Greater CPAP use was associated with a favorable trend for improvement in the modified Rankin score, a measure of functional ability: a 0.3-point reduction with no or poor CPAP use, a 0.4-point decrease with some use, and a 0.9-point reduction with good use.

The encouraging results will be helpful in designing a planned much larger, event-driven, definitive phase III trial, Dr. Yaggi said.

Dr. Yaggi had no financial conflicts regarding this National Heart, Lung and Blood Institute-sponsored study.

bjancin@frontlinemedcom.com

acute MI, stroke, hospitalization for unstable angina, or urgent coronary revascularization, was 13.1 per 100 person-years with usual care and 11.0 in the CPAP intervention arms. While these results are encouraging, SLEEP TIGHT wasn't powered to show significant differences in these hard events.

Outcomes across the board didn't differ significantly between the CPAP and enhanced CPAP groups. And since the mean number of hours of CPAP use per night was also similar in the two groups – 3.9 hours with standard CPAP and 4.3 hours with enhanced CPAP – it's likely that the phase III trial will rely upon the much simpler standard CPAP intervention, according to Dr. Yaggi.

He deemed CPAP adherence in this stroke/TIA population to be similar to the rates typically seen in routine sleep medicine practice. Roughly 40% of the stroke/TIA

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

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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Helmets cut intubation rates

NIV from page 1

cers in 7% of the helmet group.

The study population included adults aged 18 years and older who were admitted to the ICU at the University of Chicago between September 2012 and September 2015 and required face mask NIV.

The most common causes of acute respiratory failure in both patient groups were pneumonia and pneumonia that was caused by immunosuppression.

The study results were limited by several factors including a lack of blinding, the need for a learning curve for clinicians using the helmet, and the potential for patient-ventilator dyssynchrony in the helmet group, noted Dr. Bhakti K. Patel of the University of Chicago and her colleagues (JAMA 2016;315:2435-41).

Multicenter studies are needed to

support the findings, they added. However, the findings “affirm the far-reaching benefits of spontaneous yet highly supported ventilation in an



awake, animated patient over invasive medical ventilation via endotracheal tube,” they wrote.

“These findings warrant further investigation of helmet NIV for patients with ARDS and other types of AHRF [acute hypoxemic respiratory failure], particularly with attention to

long-term outcomes,” the researchers wrote.

The researchers had no financial conflicts to disclose.

In a related study published in the Journal of Cardiothoracic and Vascular Anesthesia, patients treated with noninvasive positive pressure ventilation (NPPV) through helmets had significantly lower heart rates,



COURTESY DR. BHAKTI PATEL

The long-term outcomes of helmet NIV for patients with ARDS and other types of acute hypoxemic respiratory failure need to be studied, said Dr. Patel.

lower average arterial pressure, and improved left ventricular ejection fraction at the end of treatment, compared with patients treated with ventilation masks and controls. Dr. Yi Yang of Capital Medical University in Beijing, China, and colleagues conducted the prospective study of 75 adults experiencing hypoxemia within 24 hours of extubation after Stanford type A aortic dissection. The

participants were divided into three 25-patient groups. The control group was treated with high-flux inhalation of oxygen via a Venturi mask, another group was treated with NPPV via a mask, and the third group was treated with NPPV via a helmet. (J Card Vasc Anesth. 2016. <http://dx.doi.org/10.1053/j.jvca.2016.03.129>).

The study was funded by China's public welfare industry of health.

VIEW ON THE NEWS

More research needed on helmet NIV

Dr. Eric J. Gartman, FCCP, comments: While we all got a good laugh at the [appearance of the] helmet itself, this study certainly produced very impressive results. This study is important, because if there is a way to improve the compliance and efficacy of noninvasive ventilation, and, thus, yielding the multiple benefits of avoiding endotracheal intubation and prolonged mechanical ventilation, it should be aggressively implemented.

The proposed mechanism for improved efficacy of these helmets is the preservation of

applied pressures and avoidance of air leak. If the helmets do allow clinicians both to be able to increase airway pressures above levels they typically would with mask-NIV and maintain those pressures without unpredictable system leak, that would be of great physiologic importance for patients with acute respiratory failure.

While the results of this study are very impressive, it is a single-center study. Obviously, a larger multicenter trial, with all types of institutions included - not just large academic centers - would

be helpful to elucidate the benefits of this technique and support a change in the standard of care in the use of NIV.

A change to this system would be a very large culture shift in NIV, and would mean a significant amount of training [for physician, nursing, and respiratory care professionals], purchasing the helmets, and ensuring that it is implemented properly and safely. As stated by the authors, this fact is similar to the change that occurred originally with NIV - but if their results reflect a true benefit over FM-NIV, such a large change would certainly be worth the effort.



“I'd like to see (these results) replicated, because in the U.S., for example, this medication isn't even available,” said Dr. David Mannino, FCCP.

FRONTLINE MEDICAL NEWS

Annual exacerbation rate lower

COPD from page 1

the trial's primary endpoint of noninferiority, but also established superiority.

The dual bronchodilator combination was also superior to salmeterol-fluticasone when it came to other outcomes, such as respiratory-related health status and rescue medication use, and it had a good safety profile.

“I think we can say that... a dual bronchodilator is the first-choice combination that can be used in patients with COPD,” commented lead author Dr. Jadwiga A. Wedzicha, a professor of respiratory medicine at the National Heart and Lung Institute, Imperial College London.

“This has a lot of implications. We are going to have to rewrite the guide-

lines and change our algorithms,” she said, noting that a LABA with an inhaled corticosteroid (the latter of which has adverse effects, especially in an aging population) or single-agent LAMA is currently recommended. “I'm pretty convinced by the data. We've got basically four LABA-LAMAs out there; we need to see other studies and look at different patient populations. But I think the data is pretty persuasive, so that we can now change our algorithms.”

Several ongoing studies are looking at triple therapy of a LABA-LAMA plus an inhaled corticosteroid, which may be useful in patients who continue to

Continued on page 10



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Indications ProAir RespiClick® (albuterol sulfate) Inhalation Powder is indicated in patients 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Important Safety Information

- ProAir RespiClick® (albuterol sulfate) Inhalation Powder is contraindicated in patients with hypersensitivity to albuterol or patients with a severe hypersensitivity to milk proteins. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose
- ProAir RespiClick® can produce paradoxical bronchospasm that may be life-threatening. Discontinue ProAir RespiClick® and institute alternative therapy if paradoxical bronchospasm occurs
- Need for more doses of ProAir RespiClick® than usual may be a marker of acute or chronic deterioration of asthma and requires reevaluation of treatment
- ProAir RespiClick® alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids
- ProAir RespiClick®, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. If such effects occur, the drug may need to be discontinued
- ProAir RespiClick®, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), convulsive disorders, hyperthyroidism, and diabetes
- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. Do not exceed the recommended dose

References: 1. ProAir RespiClick Prescribing Information. Horsham, PA: Teva Respiratory, LLC; April 2016. 2. ProAir RespiClick Patient Information Leaflet. Horsham, PA: Teva Respiratory, LLC; April 2016.



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Important Safety Information (continued)

- Immediate hypersensitivity reactions may occur. Discontinue ProAir RespiClick® immediately
- ProAir RespiClick® may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants
- In controlled studies of ProAir RespiClick® in patients 12 years of age and older, adverse events that occurred at an incidence rate of at least 1% and greater than placebo included back pain (2% vs 1%), pain (2% vs <1%), gastroenteritis viral (1% vs <1%), sinus headache (1% vs <1%), and urinary tract infection (1% vs <1%)
- In controlled studies of ProAir RespiClick® in patients 4 to 11 years of age, adverse events that occurred at an incidence rate of at least 2% and greater than placebo included nasopharyngitis (2% vs 1%), oropharyngeal pain (2% vs 1%), and vomiting (3% vs 1%)

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

For more information visit ProAir.com

Continued from page 7

have exacerbations on dual bronchodilator therapy, according to Dr. Wedzicha. "I think we'll move to the triple [therapy], because breathlessness is a problem," she predicted, noting that bronchodilators address that symptom well. "As you get more

severe, you are going to get short of breath. So I think the LABA-LAMA will stay and the inhaled corticosteroid will be added on top. That's what I think COPD treatment will look like."

Press conference moderator Dr. David Mannino, professor & chair (Preventive Medicine & Environ-

mental Health) at the University of Kentucky College of Public Health in Lexington, praised the research but disagreed about its implications. "I think one very good study is just that – one very good study. Is that enough to change guidelines? I don't think so," he said in an interview. "I'd like to see this replicated, because in

the U.S., for example, this medication isn't even available. And if I write [a prescription] for one LABA-LAMA, what a patient actually gets may be dictated by their insurance and coverage and other things."

"So I would like to see this done with other LABA-LAMAs, and see other head-to-head trials," he elab-

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR ProAir RespiClick® (albuterol sulfate) Inhalation Powder
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR RESPICLICK (albuterol sulfate) inhalation powder is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR RESPICLICK is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

4 CONTRAINDICATIONS

Use of PROAIR RESPICLICK is contraindicated in patients with a history of hypersensitivity to albuterol and/or severe hypersensitivity to milk proteins. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate. There have been reports of anaphylactic reactions in patients using inhalation therapies containing lactose [see Warnings and Precautions (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR RESPICLICK can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR RESPICLICK should be discontinued immediately and alternative therapy instituted.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR RESPICLICK, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

5.3 Use of Anti-Inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, eg, corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR RESPICLICK, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR RESPICLICK at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR RESPICLICK, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. PROAIR RESPICLICK contains small amounts of lactose, which may contain trace levels of milk proteins. Hypersensitivity reactions including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of therapies containing lactose (lactose is an inactive ingredient in PROAIR RESPICLICK). The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR RESPICLICK.

5.7 Coexisting Conditions

PROAIR RESPICLICK, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR RESPICLICK may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR RESPICLICK may be associated with the following:

- Paradoxical bronchospasm [see Warnings and Precautions (5.1)]
- Cardiovascular Effects [see Warnings and Precautions (5.4)]
- Immediate hypersensitivity reactions [see Warnings and Precautions (5.6)]
- Hypokalemia [see Warnings and Precautions (5.8)]

ProAir RespiClick® (albuterol sulfate) Inhalation Powder

6.1 Clinical Trials Experience

A total of 1289 subjects were treated with PROAIR RESPICLICK during the clinical development program. The most common adverse reactions ($\geq 1\%$ and $>$ placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. 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.

Adults and Adolescents 12 years of Age and Older: The adverse reaction information presented in Table 1 below concerning PROAIR RESPICLICK is derived from the 12-week blinded treatment period of three studies which compared PROAIR RESPICLICK 180 mcg four times daily with a double-blinded matched placebo in 653 asthmatic patients 12 to 76 years of age.

Table 1: Adverse Reactions Experienced by Greater Than or Equal to 1.0% of Adult and Adolescent Patients in the PROAIR RESPICLICK Group and Greater Than Placebo in three 12-Week Clinical Trials¹

Preferred Term	Number (%) of patients	
	PROAIR RESPICLICK 180 mcg QID N=321	Placebo N=333
Back pain	6 (2%)	4 (1%)
Pain	5 (2%)	2 (<1%)
Gastroenteritis viral	4 (1%)	3 (<1%)
Sinus headache	4 (1%)	3 (<1%)
Urinary tract infection	4 (1%)	3 (<1%)

1. This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of greater than or equal to 1.0% in the PROAIR RESPICLICK group and greater than placebo.

In a long-term study of 168 patients treated with PROAIR RESPICLICK for up to 52 weeks (including a 12-week double-blind period), the most commonly reported adverse events greater than or equal to 5% were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia.

In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring ($\geq 5\%$) adverse events.

Pediatric Patients 4 to 11 Years of Age: The adverse reaction information presented in Table 2 below concerning PROAIR RESPICLICK is derived from a 3-week pediatric clinical trial which compared PROAIR RESPICLICK 180 mcg albuterol 4 times daily with a double-blinded matched placebo in 185 asthmatic patients 4 to 11 years of age.

Table 2: Adverse Reactions Experienced by Greater Than or Equal to 2.0% of Patients 4 to 11 Years of Age in the PROAIR RESPICLICK Group and Greater Than Placebo in the 3 Week Trial

Preferred Term	Number (%) of patients	
	PROAIR RESPICLICK 180 mcg QID N=93	Placebo N=92
Nasopharyngitis	2 (2%)	1 (1%)
Oropharyngeal pain	2 (2%)	1 (1%)
Vomiting	3 (3%)	1 (1%)

6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with PROAIR RESPICLICK, the following adverse events have been reported during use of other inhaled albuterol sulfate products: Urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (potentially fatal), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. 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.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic bronchodilators should not be used concomitantly with PROAIR RESPICLICK. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

orated. “And there is a great deal of boldness and risk on the part of drug companies to do head-to-head trials because they might not get a win. They lucked out in this one. You could do the same trial with products from different companies and not get the same results. And then you are left wondering what was wrong.”

The 3,362 patients in FLAME had disabling, symptomatic COPD and had experienced at least one exacerbation in the past year. They were randomized evenly to once-daily indacaterol-glycopyrronium (marketed outside the United States) or twice-daily salmeterol-fluticasone.

Results showed that the annual rate

of any exacerbation was significantly lower with indacaterol-glycopyrronium than with salmeterol-fluticasone in the per protocol population (3.59 vs. 4.03; rate ratio, 0.89), with similar findings in the intent-to-treat population. Additionally, in a preplanned analysis, the findings were consistent regardless of patients’ blood levels of

eosinophils, a possible marker of steroid sensitivity.

Indacaterol-glycopyrronium was also associated with a longer time to first exacerbation (71 vs. 51 days; hazard ratio, 0.84) and a lower annual rate of moderate or severe exacerbations (0.98 vs. 1.19; rate ratio, 0.83).

There was no difference between groups in the risk of death, but the study lasted only a year and was not powered for that endpoint, Dr. Wedzicha pointed out. “We are seeing less deaths in patients generally in COPD because we are monitoring them very carefully.” Indacaterol-glycopyrronium was also superior to salmeterol-fluticasone based on scores on the St. George’s Respiratory Questionnaire, use of rescue medication, and lung function.

The indacaterol-glycopyrronium formulation available in the United States, which contains lower doses of the drugs and is used twice-daily, would likely net results similar to those seen in the trial, she speculated. However, once-daily treatment is generally associated with better compliance.

The inflammatory component of COPD still needs attention, according to Dr. Wedzicha. “There is no good evidence that a LABA-LAMA is doing anything to the underlying airway inflammation ... I think a major unmet need now is novel anti-inflammatory agents,” she said.

Dr. Wedzicha disclosed that she received nonfinancial support from Novartis during the study, as well as grant support and personal fees from various drug companies. The trial was sponsored by Novartis.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: As a disease, COPD has a significant impact on quality of life for our patients. Frequent returns to the hospital have many of us focusing on the care and support that our patients receive. As we redesign



the experience of care for our patients with COPD, this trial demonstrates that we may have another useful tool in the therapeutic armamentarium which may be of benefit to COPD patients. Improving quality of life for these patients will lessen the burden of this chronic disease.

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7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR RESPICLICK, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which 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. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR RESPICLICK.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR RESPICLICK should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of use of albuterol during pregnancy. Available data from published epidemiological studies and postmarketing case reports of pregnancy outcomes following inhaled albuterol use do not consistently demonstrate a risk of major birth defects or miscarriage. There are clinical considerations with use of albuterol in pregnant women [see *Clinical Considerations*]. In animal reproduction studies, when albuterol sulfate was administered subcutaneously to pregnant mice there was evidence of cleft palate at less than and up to 9 times the maximum recommended human daily inhalation dose (MRHDID) [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

Labor or Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR RESPICLICK for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR RESPICLICK has not been approved for the management of pre-term labor. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta₂-agonists, including albuterol.

Data

Animal Data

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure nine-tenths the maximum recommended human dose (MRHDID) for adults (on a mg/m² basis at a maternal dose of 0.25 mg/kg) and in 10 of 108 (9.3%) fetuses at approximately 9 times the MRHDID (on a mg/m² basis at a maternal dose of 2.5 mg/kg). Similar effects were not observed at approximately one-eleventh the MRHDID for adults (on a mg/m² basis at a maternal dose of 0.025 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 750 times the MRHDID (on a mg/m² basis at a maternal dose of 50 mg/kg).

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 80 times the MRHDID (on a mg/m² basis at a maternal dose of 10.5 mg/kg).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

ProAir RespiClick® (albuterol sulfate) Inhalation Powder

8.2 Lactation

Risk Summary

There are no available data on the presence of albuterol in human milk, the effects on the breastfed child, or the effects on milk production. However, plasma levels of albuterol after inhaled therapeutic doses are low in humans, and if present in breast milk, albuterol has a low oral bioavailability [see *Clinical Pharmacology* (12.3)].

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for albuterol and any potential adverse effects on the breastfed child from albuterol or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of PROAIR RESPICLICK for the treatment or prevention of bronchospasm in children 12 to 17 years of age and older with reversible obstructive airway disease is based on two 12-week clinical trials in 318 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, one long-term safety study in children 12 years of age and older, and one single-dose crossover study comparing doses of 90 and 180 mcg with albuterol sulfate inhalation aerosol (ProAir® HFA) in 71 patients [see *Clinical Studies* (14.1)]. The safety and effectiveness of PROAIR RESPICLICK for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 38 patients age 16 and older with exercise-induced bronchospasm comparing doses of 180 mcg with placebo [see *Clinical Studies* (14.2)]. The safety profile for patients ages 12 to 17 was consistent with the overall safety profile seen in these studies.

The safety of PROAIR RESPICLICK in children 4 to 11 years of age is based on two single-dose, controlled, crossover studies: one with 61 patients comparing doses of 90 and 180 mcg with matched placebo and albuterol HFA MDI and one with 15 patients comparing a dose of 180 mcg with matched albuterol HFA MDI; and one 3-week clinical trial in 185 patients 4 to 11 years of age with asthma comparing a dose of 180 mcg four times daily with matched albuterol HFA MDI. The effectiveness of PROAIR RESPICLICK in children 4 to 11 years with exercise-induced bronchospasm is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR RESPICLICK 90 mcg and 180 mcg with placebo in 61 patients with asthma, and data from a 3-week clinical trial in 185 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol 4 times daily with placebo [see *Clinical Studies* (14.1)].

The safety and effectiveness of PROAIR RESPICLICK in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR RESPICLICK did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy [see *Warnings and Precautions* (5.4, 5.7)].

All beta₂-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdose are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR RESPICLICK.

Treatment consists of discontinuation of PROAIR RESPICLICK together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdose of PROAIR RESPICLICK.



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PRS-40633 05/16

This brief summary is based on the ProAir RespiClick full prescribing information dated April 2016.

Nighttime extubations linked to poorer outcomes

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Mechanically ventilated patients in the intensive care unit (ICU) have poorer outcomes if extubated during the night instead of during the day, based on a retrospective cohort study reported at an international conference of the American Thoracic Society.

Overall, 20% of the nearly 98,000 adult patients studied were extubated during nighttime hours, between 7:00 p.m. and 7:00 a.m., according to data presented in a session and a related press conference.

Compared with patients extubated during daytime hours, patients extubated during nighttime hours had higher rates of ICU and hospital death, with the absolute difference ranging from 1% to 5%. Additionally, among those mechanically ventilated for at least 12 hours, nighttime extubation was associated with an absolute 2% increase in the risk of reintubation.

“I think this is the first large-scale study that looks at a practice that, although not as common as we thought it was, is still done about a fifth of the time and even with decreasing rates, is not a rare practice on our units,” commented lead author Dr. Hayley B. Gershengorn of the department of medicine (critical care) and the Saul R. Korey department of neurology at the Albert Einstein College of Medicine, New York.

“As we have increasing staffing [overnight] and maybe an increasing push to move people through our ICUs, we need to probably take some care because although we can’t demonstrate a causal link, it is quite concerning, this consistent finding of increased mortality and reintubation in these folks,” she said.

There are several possible reasons for the observed heightened risks of death and reintubation with nighttime extubation that could not be fully explored in the study, Dr. Gershengorn said.

“We were not able to identify the indication for extubation or discontinuation of mechanical ventila-

tion. So one of the concerns that we have is that it’s probably more common that folks unintentionally extubate themselves or someone unintentionally extubates them overnight, when staffing is less,” she explained. “The other part, which we tried to adjust for but we don’t have perfect data on, is what is the staffing overnight,” including factors such as the ratio of nurses to patients and how many units an intensivist is covering, not just whether he or she is present.

“In terms of the reintubation risk being higher in the [group with longer duration of mechanical ventilation], the question I have is whether or not there is less comfort with somebody looking less well when there is less staff around, and whether or not there may be a quicker trigger to reintubate them if they don’t look so great,” she said.

The majority of intubated patients are unlikely to improve enough physiologically to prompt nighttime extubation rather than waiting until daytime, according to Dr. Gershengorn. But there are at least two groups whom clinicians might want to extubate at night.

One group is those who underwent elective surgery during the day. “They are waiting to come out of anesthesia, and the plan is to discontinue mechanical ventilation at the time that that occurs,” she explained. Another group is those who are agitated on the ventilator, require more sedation than usual, and suddenly awake at night. “These patients are really hard to keep comfortable. I can [sedate them] again and try this problem all over again tomorrow morning, or I can just bite the bullet and pull the tube out,” she said.

The investigators analyzed data from the Project IMPACT critical care medicine database, in which data are prospectively collected for benchmarking purposes. In all, they studied 97,844 mechanically ventilated adults from 165 medical and surgical ICUs across the United States between 2000 and 2009.

Results showed that nighttime extubation was more common among elective surgical patients, those coming from the operating room or a postanesthesia care unit, and those mechanically venti-

lated for less than 12 hours.

In a finding that Dr. Gershengorn described as surprising, there was a temporal trend by which the adjusted proportion of extubations performed at night actually decreased in more recent years during the study period.

The investigators next looked at outcomes among 10,279 propensity-matched pairs of patients, one member of the pair having been extubated during the night and the other having been extubated during the day.

Among those mechanically ventilated for less than 12 hours, nighttime extubation was associated with higher ICU mortality (5.6% vs. 4.6%; $P = .025$) and hospital mortality (8.3% vs. 7.0%; $P = .014$). Findings were inconsistent for length of stay, with nighttime extubation associated with a shorter ICU stay but a longer hospital stay.

Among patients mechanically ventilated for 12 hours or longer, those extubated during the night had a higher rate of reintubation (14.6% vs. 12.4%; P less than .001), as well as higher ICU mortality (11.2% vs. 6.1%; P less than .001) and hospital mortality (16.0% vs. 11.1%; P less than .001). Lengths of stay did not differ by extubation time of day in this group.

In sensitivity analyses, findings were similar when the definition of nighttime extubation was altered to the hours of midnight to 5 a.m. and when analyses were restricted to nonpalliative patients, according to Dr. Gershengorn.

The lead author disclosed that she had no relevant conflicts of interest.



Patients extubated at night had higher rates of ICU and hospital death, with the absolute difference ranging from 1% to 5%, Dr. Gershengorn said.

FRONTLINE MEDICAL NEWS

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments:

This is an interesting study, but we are left without some important information. What extubation criteria were met for any/all patients, regardless of the time of day of extubation? What type of nocturnal physician staffing was available? Were extubation protocols used, or was the extubation decision made by a bedside physician? One would like to see additional information before concluding that nocturnal extubation is definitely hazardous.



Nonbenzodiazepines reduced time to extubation

BY BRIAN HOYLE
Frontline Medical News

FROM CHEST

The nonbenzodiazepines propofol and dexmedetomidine reduce the time to extubation, compared with benzodiazepines, suggest results of an observational study published in *Chest*.

“This study found that sedatives vary in their associations with

[ventilator-associated events] and time to extubation but not in their associations with time to hospital discharge or mortality. Both propofol and dexmedetomidine were associated with less time to extubation, compared with benzodiazepines,” wrote Dr. Michael Klompas of the department of population medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute, both

in Boston, and colleagues (*Chest*. 2016 Jun;149[6]:1373-9).

Current sedation guidelines for mechanical ventilation recommend using nonbenzodiazepines to lightly sedate patients, whenever possible.

Compared with the use of benzodiazepines, the uses of propofol and dexmedetomidine were associated with shorter times to extubation with hazard ratios of propofol

vs. benzodiazepines and dexmedetomidine vs. benzodiazepines of 1.4 (P less than .0001) and 2.3 (P less than .0001), respectively. In the relatively few cases involving uses of dexmedetomidine that were available, this sedative was also associated with shorter time to extubation, compared with propofol (HR, 1.7; P less than .0001).

Uses of benzodiazepines and

Continued on following page

Continued from previous page

propofol were associated with increased risk for ventilator-associated events (VAEs), compared with regimens not involving them; for benzodiazepine use, the HR was 1.4 ($P = .002$) and for propofol, the HR was 1.3 ($P = .003$). Dexmedetomidine use, in contrast, was not associated with increased risk for VAEs ($P = .92$).

Regarding hazards for hospital discharges and hospital deaths,

Both propofol and dexmedetomidine were associated with less time to extubation, compared with benzodiazepines.

using each sedative or sedative class studied had similar outcomes.

The observational study involved 9,603 retrospectively identified mechanical ventilations.

All consecutively occurring invasive mechanical ventilations lasting 3 days or longer in Boston's Brigham and Women's Hospital between July 1, 2006 and December 31, 2013 were studied.

The researchers evaluated the impact that daily use of propofol, dexmedetomidine, and benzodiazepines have on VAEs, time to extubation, time to hospital discharge, and death in a large cohort of patients.

This study's findings were similar to those of prior randomized controlled trials, especially concerning the time to extubation, the researchers said. "The large number

of episodes of mechanical ventilation in our trial dataset, however, allowed us to extend conceivable but underpowered signals from randomized controlled trials."

A limitation of this study is that it was a single-center retrospective analysis, which may have caused some of its findings to be attribut-

able to "residual confounding and/or idiosyncratic local practice patterns."

Other limitations include the lack of measurements of patients' total doses or adjusted doses per kilogram of body weight, a possible overtraining of the analysis model used to adjust for severity of

illness, and a relatively low number of patients treated with dexmedetomidine, with most of such patients undergoing cardiac surgery.

Funding was provided by the Centers for Disease Control and Prevention.

Dr. Klompas and the other researchers had no disclosures.

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity

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Introduce prostacyclin treatment early with Orenitram, which enables you to adjust dose based on tolerability and clinical response.

The only prostacyclin analogue in a tablet:

For PAH, a **progressive disease**¹⁻³ | **Early use in FC II and III**¹ | **Ability to transition from treprostinil parenteral therapy**^{1*}

Orenitram allows you to initiate treatment with 0.125 mg TID (~8 hrs apart) or 0.25 mg BID (~12 hrs apart), then titrate up or down every 3 to 4 days as needed. In the pivotal trial, dose was titrated based on clinical response and tolerability. If not tolerated, titrate slower or decrease dose by 0.25 mg. Avoid abrupt discontinuation. Orenitram tablets should be taken whole and with food. If a dose is missed, please refer to the Full Prescribing Information. Orenitram should not be used in patients with moderate hepatic impairment. Dose adjustments required for mild hepatic impairment.

*In a 24-week, multicenter, open-label study to establish safety and tolerability of transition, WHO Group 1 patients (FC I or II) on stable doses of IV/SC treprostinil as well as a PDE-5i and/or ERA were evaluated.

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

OREIS1hcpJAN16

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

For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

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- McLaughlin V et al. ACCF/AHA 2009 expert consensus on pulmonary hypertension: developed in collaboration with the ACCP, ATS, and the PHA. *Circulation*. 2009;119(16):2250-2290.

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: As physicians and other health-care prescribers, we must remember that the pharmacokinetics of the medications that we prescribe are important to keep in mind as we are selecting those medications to achieve certain effects (in the study cited, sedation) in the process of care delivery. Careful consideration of the patient's physiology, pathophysiology, and therapeutic goals, along with an understanding of the pharmacokinetics of the medications we chose, should guide our medication selection practices.

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EXTENDED-RELEASE TABLETS
dosing that adapts.

Midodrine cuts ICU days in septic shock patients

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST

Septic shock patients who received midodrine needed significant-

ly fewer intravenous vasopressors during recovery and had shorter hospital stays, based on data from a retrospective study of 275 adults at a single tertiary care center.

In many institutions, policy dictates

that patients must remain in the ICU as long as they need intravenous vasopressors, wrote Dr. Micah R. Whitson of North Shore-LIJ Health System in New Hyde Park, N.Y., and colleagues. "One solution to this

problem may be replacement of IV vasopressors with an oral agent."

"Midodrine facilitated earlier patient transfer from the ICU and more efficient allocation of ICU resources," the researchers wrote (Chest. 2016;149[6]:1380-83).

The researchers compared data on 135 patients treated with midodrine in addition to an intravenous vasopressor and 140 patients treated with an intravenous vasopressor alone.

Overall, patients given midodrine received intravenous vasopressors for 2.9 days while the other group received intravenous vasopressors for 3.8 days, a significant 24% difference. Hospital length of stay was not significantly different, averaging 22 days in the midodrine group and 24 days in the intravenous vasopressor-only group. However, ICU length of stay averaged 7.5 days in the midodrine group and 9.4 days in the vasopressor-only group, a significant 20% reduction. Further, the midodrine group was significantly less likely to reinstitute intravenous vasopressors than the intravenous vasopressor-only group (5.2% vs. 15%, respectively). ICU and hospital mortality rates were not significantly different between the two groups, Dr. Whitson and associates reported.

Patients in the midodrine group received a starting dose of 10 mg every 8 hours, which was increased incrementally until they no longer needed intravenous vasopressors. The maximum midodrine dose in the study was 18.7 mg every 8 hours, and the average duration of use was 6 days.

The patients' average age was 65 years in the intravenous vasopressor group and 69 years in the midodrine group. Other demographic factors did not significantly differ between the two groups.

One patient discontinued midodrine before discontinuing an intravenous vasopressor because of bradycardia, which resolved without additional treatment.

The findings were limited by the observational nature of the study and the use of data from a single center, the investigators noted. The results, however, support the safety of midodrine and the study "lays the groundwork for a prospective, randomized controlled trial that will examine efficacy, starting dose, escalation, tapering and appropriate patient selection for midodrine use during recovery from septic shock," they said.

The researchers had no financial conflicts to disclose.



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treprostinil

EXTENDED-RELEASE TABLETS

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS

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

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

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

ADVERSE REACTIONS

Clinical Trials Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, diarrhea, nausea and flushing. Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

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

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%

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.

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

Labor and Delivery—The effect of Orenitram on labor and delivery in humans is unknown.

No treprostinil treatment related effects on labor and delivery were seen in animal studies.

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

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

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

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

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

OVERDOSAGE

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

United Therapeutics Corporation, Research Triangle Park, NC 27709
Rx only
January 2016
www.orenitram.com



Renal replacement delay may benefit critically ill

BY SUSAN LONDON
Frontline Medical News

SAN FRANCISCO – Delaying renal replacement therapy in critically ill patients with severe acute kidney injury appears to be not only safe but beneficial, based on a randomized controlled trial conducted in France.

The trial, Artificial Kidney Initiation in Kidney Injury (AKIKI), was conducted among 620 adult patients from 31 intensive care units and was led by Dr. Stéphane Gaudry of Assistance Publique–Hôpitaux de Paris.

The death rate did not differ for groups assigned to an early versus a late initiation strategy, according to results presented at an international conference of the American Thoracic Society and simultaneously published (*N Engl J Med.* 2016 May 15. doi: 10.1056/NEJMoa1603017).

Moreover, nearly half of the patients in the delayed initiation group were able to avoid renal replacement therapy. And they were less likely to develop bloodstream infections and had more rapid onset of diuresis (heralding recovery of renal function) than did peers in whom the therapy was initiated early.

“Our study should not be interpreted as suggesting that a ‘wait and see’ approach is safe for all patients. Indeed, careful surveillance is mandatory when deciding to delay renal-replacement therapy in patients with severe acute kidney injury so that any complications will be detected and renal-replacement therapy initiated without delay,” the researchers said.

Further, the “findings may not be generalizable, because more than 50% of the patients in our trial received intermittent hemodialysis as the first method of therapy and only 30% of the patients

received continuous renal-replacement therapy as the sole method (with no intermittent dialysis at any time).”

The author of an accompanying editorial, Dr. Ravindra L. Mehta of the University of California, San Diego, lists some caveats in interpreting the trial’s findings as support for the delayed initiation strategy.

For example, he notes, the longer time to initia-

“Our study should not be interpreted as suggesting that a ‘wait and see’ approach is safe for all patients ... careful surveillance is mandatory when deciding to delay renal-replacement therapy,” said Dr. Gaudry and colleagues.

tion with the delayed strategy contributed to worsening of metabolic and clinical status in the patients who ultimately did need therapy; the study did not assess the development of chronic kidney disease; and the types of renal replacement therapy selected for patients seem “surprising” as the majority put on this therapy needed vasopressors.

“The findings highlight a need for dynamic risk-stratification tools to identify patients who will not need renal-replacement therapy for management of their acute kidney injury,” Dr. Mehta concluded, noting that ongoing studies should help inform management in this area. “Meanwhile, we should focus on the timely application of renal-replacement therapy while considering individual patient characteristics, process-of-care elements, and logistics to achieve therapeutic goals ...”

Patients were eligible for the trial if they had

severe acute kidney injury, defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 3; required mechanical ventilation, catecholamine infusion, or both; and did not have a potentially life-threatening complication related to renal failure.

In those assigned to the early strategy, renal replacement therapy was started immediately after randomization. In those assigned to the delayed strategy, it was started if any of several criteria was met: severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 112 mg/dL, or oliguria for more than 72 hours after randomization. The specific type of renal replacement therapy was left up to each study site.

The median time between randomization and initiation of renal replacement therapy was 2 hours in the early strategy group and 57 hours in the delayed strategy group.

The estimated 60-day mortality rate – the primary outcome – was 48.5% with early initiation of therapy and 49.7% with delayed initiation, a nonsignificant difference. Fully 49% of the delayed strategy group never received renal replacement therapy. Also, patients in this group were half as likely as were peers in the early initiation group to develop a bloodstream infection (5% vs. 10%), and they had more rapid onset of diuresis (*P* less than .001).

The groups were essentially the same with respect to the rate of gastrointestinal bleeding and the lengths of stay in the intensive care unit and in the hospital.

Dr. Gaudry disclosed that he received grant support from the French Ministry of Health during the study, and from XENIOS France outside the research. The trial was supported by a grant from Programme Hospitalier de Recherche Clinique National, 2012 (AOM12456), funded by the French Ministry of Health.

Hospital-acquired RVIs drive up in-hospital death rate

BY KARI OAKES
Frontline Medical News

BOSTON – Hospital-acquired respiratory viral infections may be a significant and underappreciated cause of morbidity and mortality among hospitalized patients.

According to a multisite, retrospective chart review of 44 patients with hospital-acquired respiratory viral illnesses (HA-RVIs), 17 patients (39%) died in-hospital. Further, of the 27 who survived, 18 (66.6%) were discharged to an advanced care setting rather than to home, though just 11/44 (25%) had been living in an advanced care setting before admission.

For hospitalizations complicated by HA-RVI, the average length of stay was 30.4 days, with a positive respiratory virus panel (RVP) result at a mean 18 days after admission.

“HA-RVIs are an underappreciated event and appear to target the sickest

patients in the hospital,” said coauthor Dr. Matthew Sims, director of infectious diseases research at Beaumont Hospital, Rochester, Mich., at a poster session of the annual meeting of the American Society of Microbiology.

First author Dr. Adam K. Skrzynski, also of Beaumont Health, and his coauthors performed the analysis of 4,065 patients with a positive RVP result during hospitalization at a regional hospital system in the September 2011-May 2015 study period; the 1.1% of patients with positive results who formed the study cohort had to have symptoms of a respiratory infection occurring after more than 5 days of hospitalization. Mortality data were collected for the first 33 days of hospitalization.

Positive RVP results for those included in the study came primarily from nasopharyngeal swab (*n* = 32), with the remainder from broncho-



HA-RVIs target the sickest patients, Dr. Matthew Sims said.

alveolar lavage (*n* = 11) and sputum (*n* = 1). Most patients were female (29/44, 66%), and elderly, with an average age of 74 years. In an interview, Dr. Sims said that many patients were smokers, and that chronic obstructive pulmonary disease and obesity were common comorbidities.

The prognosis was particularly grim for the 12 patients who were admitted to the ICU: 10 died after an average 9.6 days in the ICU. “Intubation didn’t help these patients,” said Dr. Sims. Nine patients were intubated within 7 days of their positive RVP results. Intubation lasted an average 7.6 days, and all nine of patients died.

The RVP came into use in 2011 and made it possible to identify if a respiratory virus was causing symptoms – and which virus was the culprit – said Dr. Sims. For the studied population, 13 of 44 patients had influenza; 11 of those had influenza A and 2 had influenza B. There were 10 positive RVP results for parainfluenza.

Dr. Skrzynski reported no outside funding source, and the study authors had no financial disclosures.

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SLEEP STRATEGIES: The flexibility of the STOP-Bang Questionnaire to screen for OSA: A practical approach

BY DR. MAHESH NAGAPPA
AND DR. FRANCES CHUNG

Obststructive sleep apnea (OSA) is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep. OSA occurs when the throat muscles intermittently relax and block the airway during sleep. The condition is usually associated with several other chronic medical conditions leading to poor quality of life.

It is estimated that at least 25 million adults are affected by OSA in the United States. Further, the obesity epidemic has increased the prevalence of OSA in the last 2 decades. The prevalence of OSA can be higher in patients undergoing surgery. For example, 70% of the patients undergoing bariatric surgery have OSA, whereas 48% of patients undergoing cardiac surgery have moderate-severe OSA. Alarmingly, in 80% of patients with moderate-severe OSA, the disorder remains undiagnosed and untreated, threatening public health and safety.

Patients with OSA can experience multiple complications when receiving sedatives and opioids during anesthesia (Oppenheimer. *Anesthesia Analgesia*. 122[5]:1321). These drugs may diminish the protective arousal reflex triggered by bouts of hypoxia, thereby increasing the risk of prolonged periods of apnea and possibly respiratory arrest.

Sedatives and narcotics can decrease pharyngeal muscle tone,

which can worsen the existing OSA and increase upper airway resistance. Undiagnosed and untreated OSA may be a contributing factor in many of these complications. Effective screening/diagnosis and treatment of OSA are considered to be important steps to reduce health-care spending, improve chronic disease management, and reduce complications.

The STOP-Bang Questionnaire

The gold standard for the diagnosis of OSA is overnight polysomnography. However, it is time consuming, labor intensive, and costly. The STOP-Bang Questionnaire is considered to be the most validated screening tool for OSA for various populations (Nagappa et al. *PLoS One*. 2015;10[12]:e0143697).

The STOP-Bang Questionnaire includes four questions used in the STOP Questionnaire plus four additional demographic queries, a total of eight dichotomous (yes/no) questions related to the clinical features of sleep apnea (Snoring, Tiredness, Observed apnea, high blood Pressure, BMI, age, neck circumference, and male gender). For each question, answering "yes" scores 1, a "no" response scores 0, and the total score ranges from 0 to 8 (see www.stop-bang.ca).

The Questionnaire can be completed quickly and easily (usually within 1-2 minutes), and the overall response rates are typically high (90%-100%). Because of its ease of use, efficiency, and high sensitivity, the STOP-Bang Questionnaire has been widely adopted in various populations, such as sleep clinics and the surgical and general population.

The STOP-Bang Questionnaire has demonstrated a high sensitivity using a cutoff score of greater than or equal to 3: 84% in detecting any sleep apnea (apnea-hypopnea index greater than 5 events/h), 93% in detecting moderate to severe sleep apnea (AHI greater than 15 events/h), and almost 100% in detecting severe sleep apnea (AHI greater than 30 events/h). The corresponding specificities were 56.4%, 43%, and 37% (Chung et al. *Anesthesiology*. 2008;108[5]:812). If patients score 0-2 on the STOP-Bang Questionnaire, they are considered to be at low risk of OSA, and the possibility of moderate to severe sleep apnea can be ruled out.

The modest specificity of the STOP-Bang Questionnaire may yield moderately high false-positive cases.

This may lead to unwanted sleep study referrals and increased health care expenditure.

There are several ways by which the specificity can be improved, thereby decreasing false-positive rates.

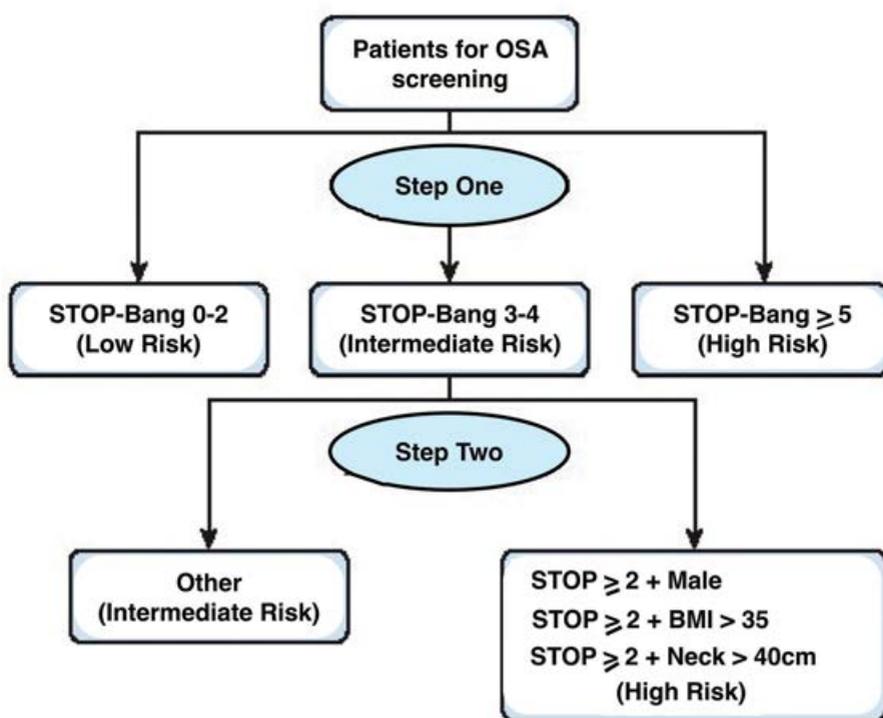
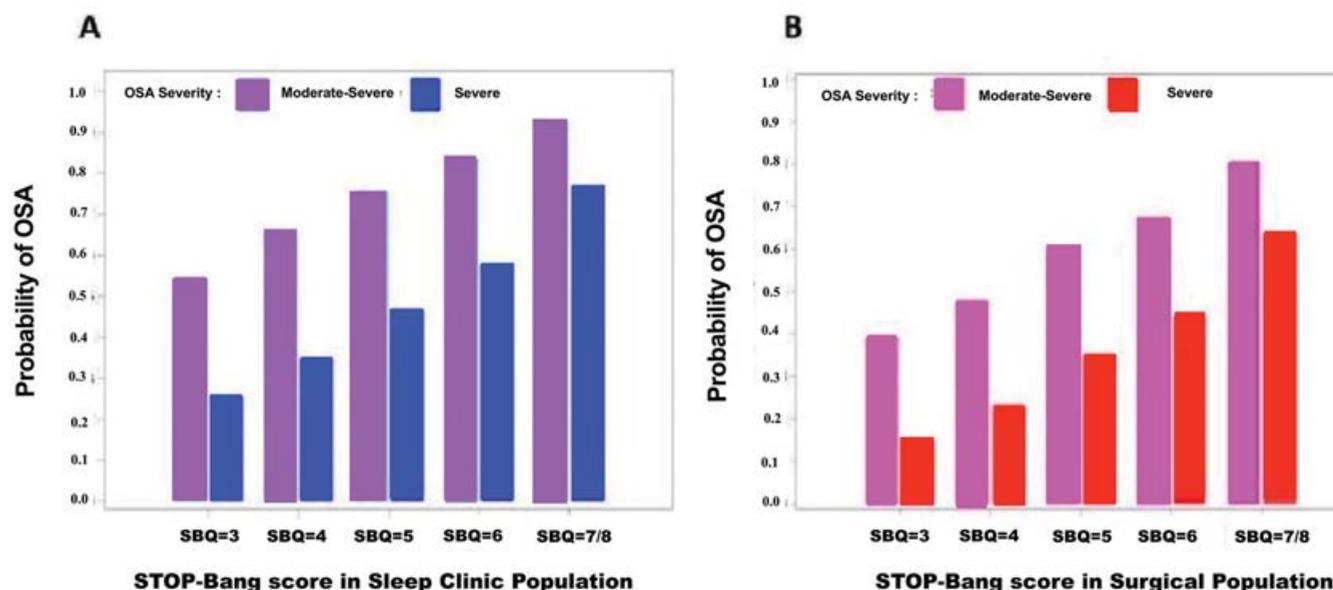
Setting a threshold for the STOP-Bang scores in different population

The main advantage of the STOP-Bang scores is its flexibility to use different scores for different populations. For example, in a bariatric population, a STOP-Bang score of greater than or equal to 4 can be used. On the other hand, in an ENT population, where we would like to identify a majority of patients with moderate-severe OSA, a STOP-Bang score of greater than or equal to 5 can be used.

In the sleep clinic population, as the STOP-Bang score cut-off increased from 3 to 8, the specificity increased from 52% to 100%, and the PPV increased continuously from 93% to 100% for any OSA (AHI greater than or equal to 5). A similar pattern was seen in the surgical population, as the STOP-Bang score cutoff increased from 3 to greater than or equal to 7, the specificity increased from 40% to 98%, and the PPV increased from 75% to 82% for any OSA (AHI greater than or equal to 5) (Nagappa et al. *PLoS One*. 2015;10[12]:e0143697).

Regional practices should decide the appropriate threshold of screening tests, after considering the implications for missed diagnoses and cost of care. There is a trade-off between sensitivity and specificity.

Continued on page 19



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Continued from page 16

At lower thresholds, there is improved sensitivity with potentially increased resource utilization, whereas increasing the threshold will result in loss of sensitivity and increased false-negative rates but improved resource utilization. A higher threshold should be adopted in the population with a lower prevalence of OSA.

STOP-Bang score and probability of OSA

In both sleep clinic patients (Fig 1; Panel A) and surgical patients (Fig 1; Panel B), the probability of moderate-to-severe OSA or severe OSA increased as the STOP-Bang score increased from 3 to 7/8. With higher scores, there is a more profound increase in the probability of severe OSA, compared with moderate OSA (Chung et al. *Br J Anaesth*. 2012;108[5]:768).

Alternative models for scoring the STOP-Bang Questionnaire

The individual items on the Questionnaire do not share an equal predictive weight for OSA. In the “Bang” components, body mass index greater than 35 kg/m², neck circumference greater than 40 cm, and male gender are more predictive than age greater than 50 years.

The predictive performance of the specific combinations of items has been explored. Compared with the specificity of 31% for detecting moderate to severe OSA, specific combinations significantly improve the specificity to detect any OSA (AHI greater than 5), moderate to severe OSA (AHI greater than 15), and severe OSA (AHI greater than 30) at the expense of sensitivity.

The specificity to detect moderate to severe OSA increases to 85% for a STOP score greater than or equal to 2 + BMI greater than 35 kg/m²; to 79% for a STOP score greater than or equal to 2 + neck circumference > greater than 40 cm (16 in); and to 77% for a STOP score greater than or equal to 2 + male, respectively.

These combinations can assist in accurately identifying more patients with moderate to severe OSA (Chung et al. *J Clin Sleep Med*. 2014;10[9]:951).

The STOP-Bang Questionnaire and serum bicarbonate

Serum bicarbonate (HCO₃⁻) is significantly correlated to AHI, and the addition of serum HCO₃⁻ greater than or equal to 28 mmol/L to a STOP-Bang score greater than or equal to 3 improves the specificity to predict moderate-severe OSA but

decreases its sensitivity (Chung et al. *Chest*. 2013;143[5]:1284).

For a STOP-Bang score of greater than or equal to 3 + HCO₃⁻ greater than or equal to 28 mmol/L, the specificity for detecting moderate to severe OSA increases from 30% to 82%, and from 28% to 80% for detecting severe OSA, respectively.

A two-step strategy for using STOP-Bang Questionnaire

A two-step algorithm using the STOP-Bang Questionnaire identifies patients effectively with a high probability of moderate to severe sleep apnea (Fig 2) (Chung et al. *Chest*. 2016;149[3]:631).

The first step is to check the STOP-

Bang score. If a patient scores 0-2 on the STOP-Bang Questionnaire, he or she is unlikely to have moderate to severe OSA. Conversely, a patient with a STOP-Bang score of 5-8 has a high probability of moderate to severe OSA.

The second step is for the patients
Continued on following page

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- 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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Continued from previous page

with STOP-Bang scores of 3 or 4.

These patients can be further classified as having a higher risk for moderate to severe OSA if one of the following conditions is met: (1) a STOP score greater than or equal to 2 + BMI greater than 35

kg/m²; (2) a STOP score that is greater than or equal to 2 + male gender; (3) a STOP score that is greater than or equal to 2 + neck circumference greater than 40 cm (16 in); or (4) a STOP-Bang score greater than or equal to 3 + serum HCO₃⁻ greater than or equal to 28 mmol/L.

The STOP-Bang Questionnaire and perioperative complications

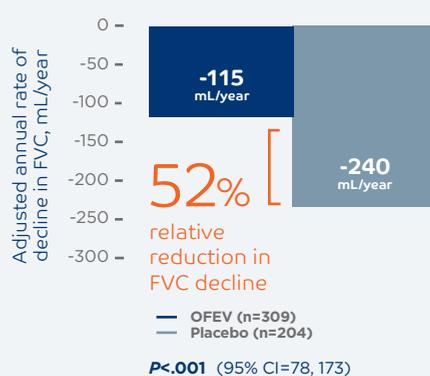
The STOP-Bang Questionnaire not only identifies the high-risk patients with OSA but also may have a strong association toward predicting perioperative complications (Vasu et al. *Arch Otolaryngol Head Neck Surg.* 2010;136[10]:1020).

The important step of screening patients with OSA using the STOP-Bang Questionnaire may create an awareness among the perioperative team resulting in decreased complications (Veenstra et al. *Crit Care Nurs Clin N Am.* 2014;26[4]:499).

The Joint Commission's Division of Healthcare Improvement has

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

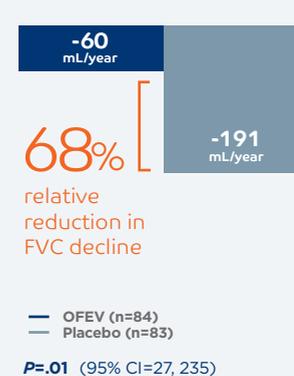
INPULSIS[®]-1 (Study 2)^{3,4}



INPULSIS[®]-2 (Study 3)^{3,4}



TOMORROW (Study 1)^{3,5}



CI, confidence interval.

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes

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

Gastrointestinal Disorders

Diarrhea

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

Nausea and Vomiting

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

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



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raised strong concerns regarding the lack of training for health-care professionals to recognize OSA. A guideline published by the Society of Anesthesia and Sleep Medicine recommends using a screening tool to identify high-risk patients with OSA (Chung et al. *Anesthesia Analgesia*. 2016;June 1: Epub ahead of print).

There is preliminary evidence that patients who have diagnosed OSA and a CPAP prescription had significantly reduced postoperative cardiovascular complications (cardiac arrest and shock) by more than 50% vs patients with undiagnosed OSA (Mutter et al. *Anesthesiology*. 2014;121[4]:707).

Conclusion

The STOP-Bang Questionnaire is a simple, practical, and flexible screening tool that is used to identify the high-risk OSA patient.

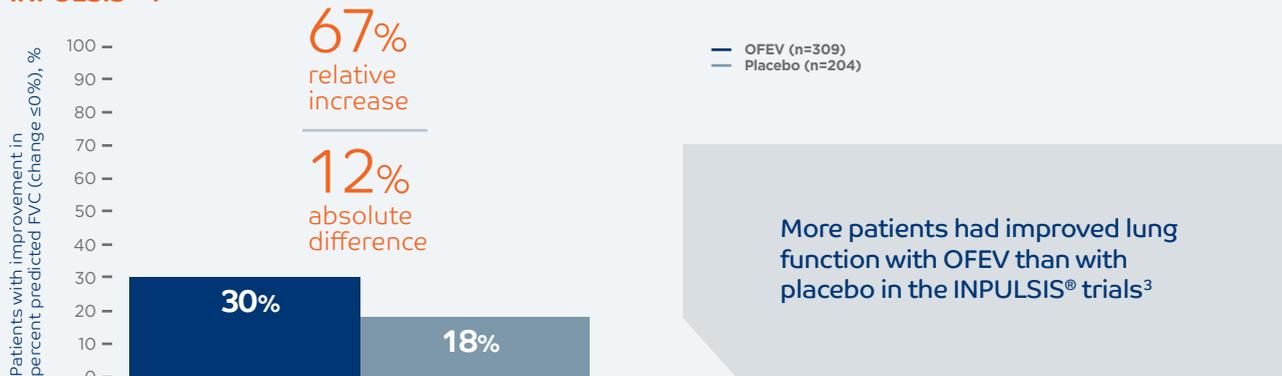
More information is available at www.stopbang.ca.

Dr. Chung is with the department of anesthesia, Toronto Western Hospital – University Health Network, University of Toronto, ON, Canada.

Dr. Nagappa is with the department of anesthesia & perioperative medicine, London Health Sciences Centre and St. Joseph Health Care London, Western University, London, ON, Canada.

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

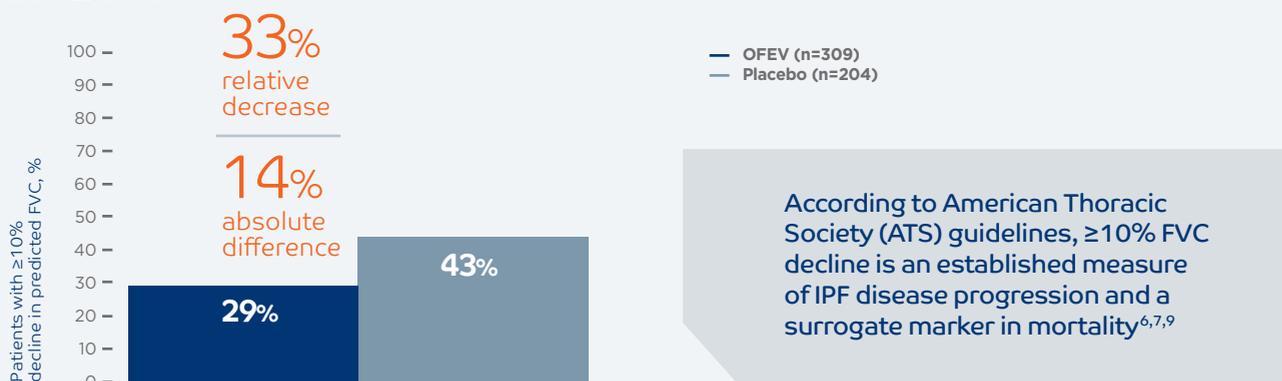
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In INPULSIS® trials, there was not a statistically significant difference in all-cause mortality for OFEV compared with placebo.³

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

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

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



USPSTF draft rec opposes asymptomatic screening

BY KATIE WAGNER LENNON
Frontline Medical News

The U.S. Preventive Services Task Force has issued a draft recommendation opposing screening

for obstructive sleep apnea (OSA) in adults who are asymptomatic for the breathing disorder.

The USPSTF's opposition is based on its determination that there is insufficient evidence to assess the bal-

ance of benefits and harms of screening for OSA in asymptomatic adults in primary care settings, giving the service an "I" grade. The recommendation and a draft evidence review are available for public comment un-

til July 11 at 8:00 p.m. EST.

The draft recommendation is the first that the USPSTF has ever made about sleep apnea, according to the draft evidence review. The recommendation "applies to asymptomatic

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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.

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adults (aged 18 years and older) and adults with unrecognized symptoms of OSA.” It does not apply to children, adolescents, pregnant women, persons presenting with symptoms of or concerns about OSA, those who are being referred for evaluation or treatment of suspected OSA, and those who have acute conditions that

The draft recommendation “applies to asymptomatic adults (aged 18 years and older) and adults with unrecognized symptoms of OSA.”

could trigger the onset of OSA.

“Reported estimates of OSA prevalence vary due to differing definitions of OSA, sampling bias, and year of study publication. A 2013 system-

atic review reported an estimated prevalence of 2%-14% based on four community-based studies, while two U.S.-based studies conducted in the 1990s reported an estimated preva-

lence of 10% for mild OSA and 3.8%-6.5% for moderate or severe OSA,” according to the recommendation.

The USPSTF was unable to find adequate evidence on the direct harms or the benefits of screening for OSA in asymptomatic populations, including their magnitude.

Continued on following page

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

CONTRAINDICATIONS: None

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

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

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

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

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

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

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

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

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

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

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

Continued from previous page

Most primary care clinicians do not routinely screen for OSA, according to the recommendation. While the Epworth Sleepiness Scale, STOP Questionnaire, STOPBang Questionnaire, Berlin Questionnaire, and Wisconsin Sleep Questionnaire

are potential screening tests for OSA, none of these questionnaires has been validated in a primary care setting.

“There is uncertainty about the clinical utility of all potential screening tools,” and the USPSTF found no studies that prospectively evaluated screening questionnaires or clinical prediction

tools to report calibration or clinical utility for improving health outcomes,” the draft evidence review said.

The USPSTF also found no studies evaluating the effect of screening for OSA on health outcomes or that directly evaluated benefits or harms of screening for OSA.

The recommendation calls for fur-

ther research on the health outcomes of screening for OSA in asymptomatic persons and the role of sleepiness in determining health outcomes.

The following are needed:

- The identification of valid and reliable clinical prediction tools that could accurately determine which asymptomatic persons (or persons with unrecognized symptoms) would benefit from further evaluation and testing for OSA.

“There is uncertainty about the clinical utility of all potential screening tools,” and the USPSTF found no studies that prospectively evaluated screening questionnaires.

- Studies that evaluate the effect of OSA treatments or interventions on health outcomes that are adequately powered and have an appropriate length of follow-up.
- Studies that evaluate whether improvement in the apnea-hypopnea index leads to improvement in health outcomes.
- More data on the natural history of mild sleep apnea.

The final evidence review will be used to inform the final USPSTF recommendation statement, which is expected to be issued later this year.

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

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

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

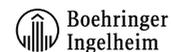
OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients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

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

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VIEW ON THE NEWS

Dr. David A. Schulman, FCCP, comments: The draft statement from the Preventive Services Task Force recommending against screening asymptomatic patients with standardized OSA questionnaires warrants a careful read.



Many sleepy patients may not complain of their fatigue unless specifically asked, choosing to attribute their symptoms to inactivity, age, weight or a lack of exercise instead of a potential underlying sleep disorder. Assessment of patients' sleep habits and patterns by primary care physicians remains a critical component of preventive health to improve identification of the twenty-plus million Americans with sleep-disordered breathing.

Lung tests limited for predicting post op outcomes

BY MARK S. LESNEY
Frontline Medical News

Routine preoperative pulmonary function tests appear to have only limited utility in predicting outcomes in patients undergoing cardiothoracic surgery when the Society of Thoracic Surgeons risk score is available, according to the results of a retrospective study.

Dr. Alexander Ivanov of New York Methodist Hospital, Brooklyn, and his colleagues conducted a database analysis of 1,685 patients undergoing index cardiac surgery at New York Methodist Hospital between April 2004 and January 2014. They used the STS risk model version 2.73 to estimate postoperative risk of respiratory failure (defined as the need for mechanical ventilation greater than or equal to 72 hours, or reintubation), prolonged postoperative length of stay (defined as greater than 14 days), and 30-day all cause mortality in these patients, according to their report in *The Journal of Thoracic and Cardiovascular Surgery* (2016;151:1183-9).

They plotted the receiver operating characteristics curve for the STS score for each of these adverse events and compared the resulting area under the curve (AUC) with the AUC after adding pulmonary function testing parameters and COPD classifications.

A total of 1,412 patients had a calculated STS score, of which 751 underwent pulmonary function testing (53%).

In general, patients who had pul-

monary function testing were older and had higher rates of comorbidities and more complex cardiothoracic surgery compared with their counterparts, according to Dr. Ivanov. These patients also had significantly elevated STS risk for prolonged ventilation (12.4% vs. 10.3%), prolonged postoperative length of stay (8.9% vs. 7.2%), and 30-day mortality (2.7% vs. 2.2%).

The decision to perform pulmonary testing was left to the treating physician. Of those patients tested, 652 had bedside spirometry and 99 had formal laboratory testing. Forced expiratory volume in 1 second (FEV₁) and forced volume vital capacity (FVC) values were determined by taking the best of three trials. COPD was diagnosed in cases of an FEV₁/FVC ratio of less than 70%.

Among these patients, 4.5% developed postoperative respiratory failure, and there was no statistically significant difference in the respiratory failure rate between patients with and without pulmonary function testing. In addition, there was no significant difference in 30-day mortality between these patients (1.9% vs. 2.1%). However, a total of 6.9% had a prolonged postoperative length of stay, with a significantly higher rate in the patients with pulmonary function testing than without (8.8% vs. 4.7%).

Dr. Ivanov and his colleagues found that the AUC of the STS score was 0.65 (95% confidence interval [CI], 0.55-0.74) for respiratory failure, 0.67 (95% CI, 0.6-0.74) for prolonged postoperative length of stay, and 0.74

VIEW ON THE NEWS

Tests define lung function severity

Chronic lung disease is one of the risk factors included in the STS model for mortality, renal failure, prolonged ventilation, sternal wound infection, reoperation, and length of hospital stay. Mild, moderate, and severe CLD increases the odds ratio for those complications. A total of 20% of almost 1 million patients used in developing the current STS risk model had CLD.

The authors found that none of the pulmonary function testing parameters added to the predictive ability of the STS risk model for operative mortality, prolonged ventilation, or prolonged length of hospital stay. Because CLD is 1 of 40 preoperative and operative variables used in the STS risk model,

an improvement in discrimination of only 1 of 40 variables is very unlikely to improve the overall model.

One may be tempted to conclude that it is not worth performing pulmonary function testing before cardiac surgery. However, remember once again the importance of precise and accurate data to support risk stratification. In science, behind each word resides a precise definition; without a pulmonary function test, we cannot define chronic lung disease severity.

Dr. Juan A. Crestanello is in the division of cardiac surgery, Wexner Medical Center, Ohio State University, Columbus. His remarks are from an invited commentary (*J Thorac Cardiovasc Surg.* 2016;151:1189-90).



(95% CI, 0.6-0.87) for 30-day mortality. Even though the STS score based upon clinical definitions of lung disease afforded only modest discriminatory ability for the three studied outcomes, they found that there was no significant added benefit to the predictive ability of these STS scores obtained by incorporating any of the pulmonary function testing parameters or COPD classifications studied.

"A possible physiological explanation for these findings may be that

the examined pulmonary function testing variables do not depend solely on pulmonary parameters such as airway diameter, degree of obstruction, or lung elasticity, but rather on a patient's effort and muscle "strength," characteristics that are already well captured and accounted for in the current STS model," the researchers stated.

The authors had no disclosures.

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Ex vivo lung perfusion may preserve lungs for more than 12 hours

BY RICHARD PIZZI
Frontline Medical News

BALTIMORE – The use of ex vivo lung perfusion (EVLP) may allow for the safe transplantation of lungs preserved for more than 12 hours, according to a study presented at the annual meeting of the American Association for Thoracic Surgery.

A research team at the University of Toronto evaluated the outcomes of transplant patients who received a lung with a preservation time of over 12 hours between January 2006 and April 2015 and compared them to the general lung transplant population.

Median hospital and ICU length of stay were similar between the two groups, and Kaplan-Meier survival curves between the two groups did not



To view our exclusive interview with Dr. Griffith, search for EVLP at www.chestphysician.org.

show any difference. Preservation time, donor PO₂, and use of EVLP were not significant variables affecting survival.

Dr. Bartley P. Griffith, chief of cardiac surgery at

the University of Maryland, Baltimore, and a discussant on the paper at the meeting, said that the findings of the study open up the possibility of a more "planned" approach to transplantation.

"Anything that not only extends preservation time, but perhaps even improves quality of preservation, would be a godsend," Dr. Griffith said in a video interview.

He cautioned that the "devil is in the details," and that the data had to be examined closely. Nevertheless, Dr. Griffith said transplant surgeons should be grateful for the important work done by the University of Toronto team.

Dr. Griffith reported that he had no relevant financial disclosures.

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24-hour BREO—Approved for Asthma

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

WARNINGS AND PRECAUTIONS (cont'd)

- 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, troleanomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS

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



BREO ELLIPTA was developed in collaboration with  Theravance

Reach for BREO

YOU WANT...

24-hour efficacy

SHE WANTS...

1 daily dose

Reach With Confidence

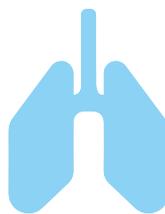
In patients uncontrolled on an ICS alone, BREO has been proven to:

Deliver 24-hour lung function improvement



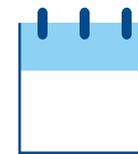
with one inhalation, once daily*

Reduce asthma exacerbations



in patients with a history of exacerbations[†]

Increase days without asthma symptoms



and increase days without use of rescue medication[‡]

Important Safety Information (cont'd)

DRUG INTERACTIONS (cont'd)

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

Supporting Clinical Study Information

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

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

[‡]In an RDB study of 1039 patients[§] symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=345) provided an increase from baseline in the % of rescue-free and the % of symptom-free 24-hour periods during the 12-week treatment period of 12.2% and 7.8%, respectively ($P \leq 0.002$), vs FF 100 mcg once daily (n=346).¹

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

References: 1. Bernstein DI et al. *J Asthma*. 2015. doi:10.3109/02770903.2015.1056350. 2. Bleecker ER et al. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561. 3. Bateman ED et al. *Thorax*. 2014;69(4):312-319.

Visit BREOhcp.com for more information, including Patient Assistance Programs.

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

BRIEF SUMMARY

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

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

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

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted.

5.2 Deterioration of Disease and Acute Episodes BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta₂-Agonists BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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

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

5.7 Transferring Patients from Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been

almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV₁ or peak expiratory flow), beta₂-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, toleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information].

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

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

5.12 Cardiovascular Effects Vilanterol, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, 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.

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

5.15 Coexisting Conditions BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and 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)]; Immunosuppression [see Warnings and Precautions (5.6)]; Hypercorticism and adrenal suppression [see Warnings and Precautions (5.8)]; Reduction in bone mineral density [see Warnings and Precautions (5.13)]. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

12-Week Trials Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years. In Trial 1, adverse reactions ($\geq 2\%$ incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

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

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

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

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

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

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

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

Cardiac Disorders Palpitations, tachycardia.

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

Musculoskeletal and Connective Tissue Disorders Muscle spasms.

Nervous System Disorders Tremor.

Psychiatric Disorders Nervousness.

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, troleanomycin, 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 beta₂-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 beta₂-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO. **Fluticasone Furoate and Vilanterol:** There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m² basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day). **Fluticasone Furoate:** There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m² basis at maternal doses up to 27 mcg/kg/day). **Vilanterol:** There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

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

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

8.3 Nursing Mothers It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and beta₂-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

8.4 Pediatric Use BREO is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established. In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/

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

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

8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

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

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

10 OVERDOSAGE

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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BREO was developed in collaboration with Theravance .



GlaxoSmithKline
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Rotor ablation for atrial fibrillation strikes out

BY M. ALEXANDER OTTO
Frontline Medical News

SAN FRANCISCO – Focal impulse and rotor modulation-guided ablation for persistent atrial fibrillation – either alone or in conjunction with other procedures – increased procedural times without improving outcomes, according to the first randomized trial to assess its utility.

In fact, enrollment in the rotor ablation-only (RA) arm was halted early for futility.

“There was 100% recurrence” of



There is no benefit to performing rotor ablation, at least with this mapping software.

DR. NATALE

atrial fibrillation, said senior investigator Dr. Andrea Natale, executive medical director of the Texas Cardiac Arrhythmia Institute, Austin.

“I’m surprised it took this long for a randomized study, because this system has been around for 5 or 6 years,” noted Dr. Natale. “Our community should demand these sorts of studies earlier, because it’s not fair for patients to go on with a procedure for years that has not been proven to be effective.”

“For us, unless there is a new version of rotor mapping that I feel is significantly different, this will be the end of rotor ablation in my lab with the system we use,” Dr. Natale said at the annual scientific sessions of the Heart Rhythm Society.

In the study, his team randomized

29 patients to RA only, 42 to RA plus pulmonary vein antral isolation (PVAI), and 42 to PVAI plus posterior wall and nonpulmonary vein trigger ablation.

At 1 year, four RA-only patients

(14%), 22 RA plus PVAI patients (52%), and 32 patients in the PVAI plus trigger group (76%) were free of atrial fibrillation and atrial tachycardias without antiarrhythmic drugs ($P < .0001$).

Meanwhile, RA alone and RA plus PVAI cases took about 230 minutes, while the more effective PVAI plus trigger approach took about 130 minutes ($P < .001$).

There was “a very poor outcome

DELAY PAH PROGRESSION TO...



INDICATION

UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

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

Please see additional Important Safety Information on adjacent page.

ADD | Upravi
selexipag
tablets | 200/1600 mcg

VIEW ON THE NEWS

Down, but not out

My gut sense is that there’s something to rotor mapping, but we are not there yet. There are a lot of investment dollars and a lot of bright people working on this. It really is the Holy Grail to find the source of atrial fibrillation.

Dr. John Day is the director of Intermountain Heart Rhythm Specialists in Murray, Utah, and the current president of the Heart Rhythm Society. He had no disclosures.

with rotor-only ablation,” Dr. Natale said. “There isn’t a benefit either alone or as an add-on strategy, at least with this mapping software.”

Perhaps “people who think rotors don’t exist are right,” he added.

On the other hand, maybe the basket mapping catheter doesn’t touch

enough of the left atrium, or the software that makes sense of what the catheter detects needs to be improved, Dr. Natale noted.

All the patients were undergoing their first ablation. They were in their early 60s, on average, and most were men.

The mean left atrium diameter was

about 47 mm, and mean left ventricle ejection fraction about 55%.

There were no statistically significant differences between the study arms.

Further, no significant differences were noted in outcomes between the 70% of patients with persistent atrial fibrillation and the 30% with

long-standing persistent atrial fibrillation.

There was no industry funding for the work. Dr. Natale disclosed relationships with Biosense Webster, Boston Scientific, Janssen, Medtronic, and St. Jude Medical.

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

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

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

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

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

PRIMARY ENDPOINT EVENTS UP TO THE END OF TREATMENT:

A primary endpoint event was experienced by 27.0% of UPTRAVI-treated patients vs 41.6% of placebo-treated patients.

Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo): hospitalization for PAH (13.6% vs 18.7%), other disease progression events (6.6% vs 17.2%)*, death (4.9% vs 3.1%), initiation of parenteral prostanoid or chronic oxygen therapy (1.7% vs 2.2%), and PAH worsening resulting in need for lung transplantation or balloon atrial septostomy (0.2% vs 0.3%).

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Adverse reactions occurring more frequently (≥3%) on UPTRAVI compared to placebo are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).

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

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

DRUG INTERACTIONS

Strong CYP2C8 inhibitors

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

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

Patients with Hepatic Impairment

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

Dosage Strengths

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

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

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

6MWD=6-minute walk distance; WHO=World Health Organization.

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

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



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Ultrasound bests auscultation for ETT positioning

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Assessment of the trachea and pleura via point-of-care ultrasound is superior to auscultation

in determining the exact location of the endotracheal tube, a randomized, single-center study found.

“It’s been reported that about 20% of the time the endotracheal tube is malpositioned,” study author Dr.

Davinder S. Ramsingh said in an interview at the annual meeting of the American Society of Anesthesiologists. “Most of the time (the tube) is too deep, which can lead to severe complications.”

In a double-blinded, randomized study, Dr. Ramsingh and his associates assessed the accuracy of auscultation vs. point-of-care ultrasound in verifying the correct position of the endotracheal tube (ETT). They enrolled 42 adults who required general anesthesia with ETT and randomized them to right main bronchus, left main bronchus, or tracheal intubation, followed by fiber optically-guided visualization to place the ETT. Next, an anesthesiologist blinded to the ETT exact location used auscultation to



DR. RAMSINGH

assess the location of the ETT, while another anesthesiologist blinded to the ETT exact location used point-of-care ultrasound to assess the location of the ETT. The ultrasound exam consisted of assessing tracheal dilation via standard cuff inflation with air and evaluation of pleural lung sliding, explained Dr. Ramsingh of the department of anesthesiology and perioperative care at the University of California, Irvine.

Dr. Ramsingh reported that in differentiating tracheal versus bronchial intubations, auscultation demonstrated a sensitivity of 66% and a specificity of 59%, while ultrasound demonstrated a sensitivity of 93% and a specificity of 96%. Limitations of the study include that “we don’t know the incidence of malpositioned endotracheal tubes in the operating room and that the patients were undergoing elective surgical procedures.” The researchers reported having no financial disclosures.

dbrunk@frontlinemedcom.com



Rx Only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

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

ADVERSE REACTIONS

Clinical Trial Experience

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

The safety of UPTRAVI has been evaluated in a long-term, placebo-controlled study enrolling 1156 patients with symptomatic PAH (GRIPHON study). The exposure to UPTRAVI in this trial was up to 4.2 years with median duration of exposure of 1.4 years. The following list presents adverse reactions more frequent on UPTRAVI (N=575) than on placebo (N=577) by $\geq 3\%$: headache 65% vs 32%, diarrhea 42% vs 18%, jaw pain 26% vs 6%, nausea 33% vs 18%, myalgia 16% vs 6%, vomiting 18% vs 9%, pain in extremity 17% vs 8%, flushing 12% vs 5%, arthralgia 11% vs 8%, anemia 8% vs 5%, decreased appetite 6% vs 3%, and rash 11% vs 8%. These adverse reactions are more frequent during the dose titration phase.

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

Laboratory Test Abnormalities

Hemoglobin

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

Thyroid function tests

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

DRUG INTERACTIONS

Strong CYP2C8 Inhibitors

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with UPTRAVI in pregnant women. Animal reproduction studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival. A slight reduction in maternal as well as in fetal body weight was observed when pregnant rats were administered selexipag during organogenesis at a dose producing an exposure approximately 47 times that in humans at the maximum recommended human dose. No adverse developmental outcomes were observed with oral administration of selexipag to pregnant rabbits during organogenesis at exposures up to 50 times the human exposure at the maximum recommended human dose.

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

Data

Animal Data

Pregnant rats were treated with selexipag using oral doses of 2, 6, and 20 mg/kg/day (up to 47 times the exposure at the maximum recommended human dose of 1600 mcg twice daily on an area under the curve [AUC] basis) during the period of organogenesis (gestation days 7 to 17). Selexipag did not cause adverse developmental effects to the fetus in this study. A slight reduction in fetal body weight was observed in parallel with a slight reduction in maternal body weight at the high dose.

Pregnant rabbits were treated with selexipag using oral doses of 3, 10, and 30 mg/kg (up to 50 times the exposure to the active metabolite at the maximum recommended human dose of 1600 mcg twice daily on an AUC basis) during the period of organogenesis (gestation days 6 to 18). Selexipag did not cause adverse developmental effects to the fetus in this study.

Lactation

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

UPTRAVI® (selexipag)

Geriatric Use

Of the 1368 subjects in clinical studies of UPTRAVI 248 subjects were 65 years of age and older, while 19 were 75 and older. No overall differences were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity cannot be ruled out.

Patients with Hepatic Impairment

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A).

A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C). Avoid use of UPTRAVI in patients with severe hepatic impairment [see Clinical Pharmacology (Pharmacokinetics)].

Patients with Renal Impairment

No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate >15 mL/min/1.73 m².

There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with glomerular filtration rates <15 mL/min/1.73 m² [see Clinical Pharmacology (Pharmacokinetics)].

OVERDOSAGE

Isolated cases of overdose up to 3200 mcg were reported. Mild, transient nausea was the only reported consequence. In the event of overdose, supportive measures must be taken as required. Dialysis is unlikely to be effective because selexipag and its active metabolite are highly protein-bound.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Specific Populations:

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

Age:

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

Hepatic Impairment:

In subjects with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, exposure to selexipag was 2- and 4-fold that seen in healthy subjects. Exposure to the active metabolite of selexipag remained almost unchanged in subjects with mild hepatic impairment and was doubled in subjects with moderate hepatic impairment. [see Use in Specific Populations].

Based on pharmacokinetic modeling of data from a study in subjects with hepatic impairment, the exposure to the active metabolite at steady state in subjects with moderate hepatic impairment (Child-Pugh class B) after a once daily regimen is expected to be similar to that in healthy subjects receiving a twice daily regimen. The exposure to selexipag at steady state in these patients during a once daily regimen is predicted to be approximately 2-fold that seen in healthy subjects receiving a twice-daily regimen.

Renal Impairment:

A 40-70% increase in exposure (maximum plasma concentration and area under the plasma concentration-time curve) to selexipag and its active metabolite was observed in subjects with severe renal impairment (estimated glomerular filtration rate ≥ 15 mL/min/1.73 m² and <30 mL/min/1.73 m²) [see Use in Specific Populations].

Drug Interaction Studies:

In vitro studies

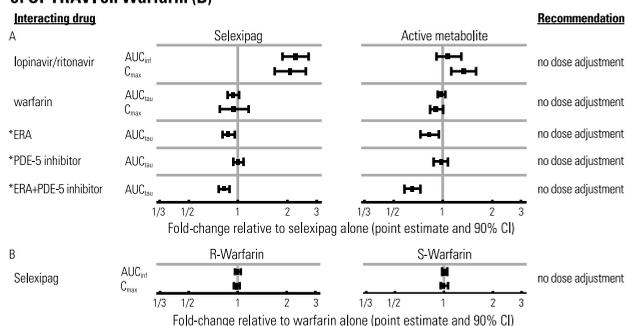
Selexipag is hydrolyzed to its active metabolite by hepatic carboxylesterase 1. Selexipag and its active metabolite both undergo oxidative metabolism by CYP2C8 and CYP3A4. The glucuronidation of the active metabolite is catalyzed by UGT1A3 and UGT2B7. Selexipag and its active metabolite are substrates of OATP1B1 and OATP1B3. Selexipag is a substrate of P-gp, and the active metabolite is a substrate of the transporter of breast cancer resistance protein (BCRP).

Selexipag and its active metabolite do not inhibit or induce hepatic cytochrome P450 enzymes at clinically relevant concentrations. Selexipag and its active metabolite do not inhibit hepatic or renal transport proteins.

The effect of strong inhibitors of CYP2C8 (such as gemfibrozil) on the exposure to selexipag or its active metabolite has not been studied. Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite [see Drug Interactions].

The results on in vivo drug interaction studies are presented in Figure 1.

Figure 1 Effect of Other Drugs on UPTRAVI and its Active Metabolite (A) and Effect of UPTRAVI on Warfarin (B)



*ERA and PDE-5 inhibitor data from GRIPHON.

Manufactured for: Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200, South San Francisco, CA 94080, USA
ACT20151221b

Reference: 1. UPTRAVI full Prescribing Information.

Actelion Pharmaceuticals US, Inc. December 2015.

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SLX-00099 0416



VIEW ON THE NEWS

Dr. Francis J. Podbielski, FCCP, comments:

Given the ubiquity of ultrasound in the operating room, generally employed to aid in placement of vascular catheters, this is a novel and very useful application of technology to ensure proper endotracheal tube placement.



IASLC proposes revising TNM classification

BY MARK S. LESNEY
Frontline Medical News

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee has developed proposals for revision of the T, N, and M categories of the 8th edition of the TNM Classification for lung cancer due to be published in late 2016. The new classification will be enacted in January 2017.

The changes proposed were based on the results of an analysis of a new database of 94,708 cases donated from 35 sources in 16 countries around the world.

The methods used and the proposals made were published in the *Journal of Thoracic Oncology* (2016;11:39-51).

Candidate proposals for the TNM stage groups were developed in conjunction with proposed changes to the T and M categories, which were previously published (*J Thorac Oncol* 2015;10:990-1003, and 2015;10:1515-22). There were no proposed changes to the N.

Changes to some T and M descriptors will result in these cases being assigned to a different stage than that to which they would have been assigned in the 7th edition. In addition, some TNM subsets have been moved to a new stage grouping, according to Dr. Peter Goldstraw of Imperial College, London, and his colleagues on behalf of the IASLC Staging and Prognostic Factors Committee.

Major new proposals

T1 changes: Size cut points have further proliferated in the proposals for the 8th edition, an outgrowth of the emphasis on tumor size in the 7th edition, such that size will now be a descriptor in all T categories, according to the authors. New stage groupings proposed divide stage T1 into T1a, T1b, and T1c, based on the new size cut points of 1 cm and 2

cm. This results in these cases (when associated with the categories N0 and M0) being assigned to stages 1A1, 1A2, and 1A3, respectively, which reflects the statistically different prognosis of these cases.

T3, T4 changes: A new group has been created for the most advanced local disease categories, T3 and T4 associated with N3 disease, but category M0. Such cases will now be classified as stage IIIC, reflecting their worse outcomes than seen in cases involving tumors that remain in stage IIIB. The prognosis for stage IIIC cases is similar to that of stage IVA cases, however the researchers justified the separation, based upon the different treatment approaches used for such cases.

M changes: Although cases with intrathoracic metastatic disease to the contralateral lung or with pleural/pericardial dissemination remain classified as M1a disease, the category M1b will now be assigned to cases with a single metastatic deposit (in one organ) and M1a and M1b cases will be moored to a new stage grouping called IVA. The more common situation of multiple metastatic deposits, usually in more than one organ, will be classified as M1c and staged as IVB. Separation of the M1a and M1b categories was maintained both for further data analysis and because some patients with oligometastatic disease are now receiving more aggressive local therapy in addition to systemic treatment, according to the authors.

Other proposals

A variety of more minor changes to stage groupings has also been proposed, some of which will result in a T descriptor being allocated to a higher stage. In some cases, tumors may be allocated to a different T category entirely, leading to a reclassification of stage. Among the examples given were tumors associated with diaphragmatic invasion to TV, which,

when associated with N0 disease, will move from stage IIB to IIA.

Impact on treatment

The relationship of the proposed classification changes to treatment decisions is not direct, the authors stated in their discussion. "Although such changes might raise the issue of whether consequent changes to treatment algorithms are needed, it is important to remind ourselves that stage does not dictate treatment. Stage is one, and perhaps the most important, of several prognostic factors that guide the appropriate treatment option[s] to offer the patient. Any change to established treatment algorithms should be based on clin-

ical judgment informed by prospective trials," they emphasized.

New stage groupings should be used in any trials of novel therapies, they added.

"We hope that the thoracic oncology community finds the proposals of value and that, when accepted, will have a positive impact on the effectiveness of treatment for lung cancer," the researchers concluded.

The research to develop the new proposals was funded by the IASLC, including funds obtained through unrestricted grants obtained from the pharmaceutical industry. The authors reported no other disclosures.

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VIEW ON THE NEWS

Mandatory reading for surgeons

The 8th edition of the TNM staging is upon us. It is the summary of analysis of 90,000 cases and data collected over 11 years. It behooves every thoracic surgeon taking care of patients with lung cancer to familiarize themselves with the new version. The staging proposal is available as an open access article on the *Journal of Thoracic Oncology* website.

From a statistical viewpoint, this edition fits the data better than previous editions did. However, from a practical application, it is more cumbersome to use routinely in a busy clinic. One hopes that we can soon say, "There's an app for that!" Such interfacing will enhance the application of this edition significantly.

The new edition of the staging system is particularly important for surgeons for two reasons. The first is the formal recognition that patients with oligometastatic dis-

ease have a better prognosis than other stage IV disease and may be amenable to multimodality therapies with curative intent, as is currently performed by select clinical teams. The second is the further refinement of stage I disease with respect to tumor size. Combined with the new histologic classification of adenocarcinoma and its proposed integration with the TNM classification, the debate of sublobar vs. lobar resection for stage I NSCLC will become more nuanced. These implications for the practicing thoracic surgeon make the manuscript mandatory reading.



Dr. Sai Yendamuri is chair, department of thoracic surgery, and director, thoracic surgery research laboratory, and a professor of oncology at Roswell Park Cancer Institute, Buffalo, N.Y. He is also the general thoracic editor for *Thoracic Surgery News*.

Giessen hybrid option for hypoplastic left heart syndrome

BY RICHARD MARK KIRKNER
Frontline Medical News

The classic Norwood palliation for infants with hypoplastic left heart syndrome (HLHS) is well established, but the procedure has drawbacks that include the need for cardiopulmonary bypass with hypothermia and it rules out biventricular correction months later. A hybrid procedure avoids the need for bypass and accommodates short-term

biventricular correction, but it has lacked strong evidence.

Researchers from Justus-Liebig University Giessen, Germany, reported on 182 patients with HLHS who had the three-stage Giessen hybrid procedure, noting 10-year survival of almost 80% with almost a third of patients requiring no artery intervention in that time (*J Thorac Cardiovasc Surg.* 2016 April;151:1112-23).

"In view of the early results and long-term out-

come after Giessen hybrid palliation, the hybrid approach has become a reasonable alternative to the conventional strategy to treat neonates with HLHS and variants," wrote Dr. Can Yerebakan and colleagues. "Further refinements are warranted to decrease patient morbidity."

The Giessen hybrid procedure uses a technique to control pulmonary blood flow that is different from the Norwood procedure. The hybrid ap-

Continued on following page

Continued from previous page

proach involves stenting of the arterial duct or prostaglandin therapy to maintain systemic perfusion combined with off-pump bilateral banding of the pulmonary arteries (bPAB) in the neonatal period. The Giessen hybrid operation defers the Norwood-type palliation using cardiopulmonary bypass that involves an aortic arch reconstruction, including a superior cavopulmonary connection or a biventricular correction, if indicated, until the infant is 4-8 months of age.

“In recent years, hybrid treatment has moved from a myth to an alternative modality in a growing number of institutions globally,” Dr. Yerebakan and colleagues said.

The hybrid procedure has been used in high-risk patients. One report claimed higher morbidity in the hybrid procedure due to bPAB (Ann Thorac Surg. 2013;96:1382-8). Another study raised concerns about an adequate pulmonary artery reha-

bilitation at the time of the Fontan operation, the third stage in the hybrid strategy (J Thorac Cardiovasc Surg. 2014;147:706-12).

But with the hybrid approach, patients retain the potential to receive a biventricular correction up to 8 months later without compromising survival, “postponing an immediate definitive decision in the newborn period in comparison with the classic Norwood palliation,” Dr. Yerebakan and coauthors noted.

The doctors at the Pediatric Heart Center Giessen treat all types and variants of HLHS with the modified Giessen hybrid strategy. Between 1998 and 2015, 182 patients with HLHS had the Giessen hybrid stage I operation, including 126 patients who received univentricular palliation or a heart transplant.

The median age of stage I recipients was 6 days, and median weight 3.2 kg. The stage II operation was performed at 4.5 months, with a range of 2.9 to 39.5 months, and Fontan completion was established at 33.7 months, with a range of 21 to 108 months.

Median follow-up after the stage I procedure was 4.6 years, and the death rate was 2.5%. After stage II, mortality was 4.9%; no deaths were reported after Fontan completion. Body weight less than 2.5 kg and aortic atresia had no significant effect on survival. Mortality rates were 8.9% between stages I and II and 5.3% between stage II and Fontan completion.

“Cumulative interstage mortality was 14.2%,” Dr. Yerebakan and colleagues noted. “At 10 years, the probability of survival is 77.8%.”

Also at 10 years, 32.2% of patients were free

from further pulmonary artery intervention, and 16.7% needed aortic arch reconstruction.

Two patients required reoperations for aortic arch reconstruction.

With the hybrid approach, patients retain the potential to receive a biventricular correction up to 8 months later without compromising survival, postponing an immediate definitive decision in the newborn period in comparison with the classic Norwood palliation.

Dr. Yerebakan and colleagues suggested several steps to improve outcomes with the hybrid approach: “intense collaboration” with anesthesiology and pediatric cardiology during and after the procedure to risk stratify individual patients; implementation of standards for management of all stages, including out-of-hospital care, in all departments that participate in a case; and liberalized indications for use of MRI before the stage II and Fontan completion.

Among the limitations of the study the authors noted were its retrospective nature and a median follow-up of only 5 years when the center has some cases with up to 15 years of follow-up.

But Dr. Yerebakan and coauthors said they could not determine if the patients benefit from the hybrid treatment in the long-term.

The researchers had no disclosures.

VIEW ON THE NEWS

Dr. Jacques-Pierre Fontaine, FCCP, comments:

This research is interesting and impactful. The hybrid operation for HLHS is a new technique not well known by North American cardiothoracic surgeons – especially ones who do not practice pediatric cardiac surgery routinely.



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Web app extended survival of lung cancer patients

BY DANIEL M. KELLER
Frontline Medical News

CHICAGO – A simple Web-based mobile application (web-app) improved survival time and quality of life of patients with advanced lung cancer, according to a randomized study presented at the annual meeting of the American Society of Clinical Oncology.

The study was stopped at the planned interim survival analysis that occurred after 121 evaluable patients because of survival benefit favoring the web-app arm. The application, called Moovcare, allowed patients to report symptoms over time and stay in close touch with their care providers after their initial surgery, chemotherapy, or radiation therapy.

“The 1-year survival was 75% in the Moovcare vs. 49% in the control arm,” said lead author Dr. Fabrice Denis of the Institut Inter-régional de Cancérologie Jean Bernard in LeMans, France, in a press conference.

Dr. Denis identified several reasons why a web-app could be useful in treating patients with lung cancer. Even with more than 1 million lung cancer deaths a year worldwide, there is no standard follow-up, and relapses do not occur on a 3 or 6-month schedule of planned visits. So patients often wait several weeks until their next visit to report symptoms indicative of a relapse. They may also be reluctant to report symptoms because of shame over how they contracted the disease, for example, from smoking. And patients are often hesitant to “bother” the doctor with symptoms between visits. All these reasons can contribute to suboptimal therapy and worse outcomes.

Moovcare was designed to allow patients to report symptoms weekly, facilitating early detection of relapse or dangerous conditions and triggering early supportive care. They compared the web-app to a control of usual, nonpersonalized follow-up in



a French multicenter prospective, randomized trial.

Patients (n = 121) with stage II/node-positive to stage IV (90% stage III/IV) nonprogressive small cell or non-small cell lung cancer were randomly assigned 1:1 to the two arms of the trial. They had to have Internet access, prior experience with email, performance status of 0-2, and an initial symptom score less than 7.

Patients could be taking tyrosine kinase inhibitors or on maintenance therapy.

The 1-year survival was 75% in the Moovcare arm vs. 49% in the control arm.

DR. DENIS

in the case of the web-app, as suggested by patient report in the algorithm.

The median follow up was 9 months. Relapse rates were close to 50% for both groups. The 1-year survival of 75% in the Moovcare to 49% in the control arm gave a 1-year absolute survival increase of 26%. Median survival was 19 months vs. 12 months, a 7-month improvement in median survival for the Moovcare arm. The hazard ratio for death in the web-app arm, compared with the control arm was 0.325 (95% confidence interval, 0.157-0.672; $P = .0025$).

When they relapsed, 77% of patients in the web-app arm had a good performance status, compared with 33% in the control arm. “This led to 74% of patients receiving optimal therapy in the Moovcare arm vs. 33% in the control arm,” Dr. Denis said. “And the number of imaging [procedures] was reduced by 50% per patient per year.”

Overall quality of life was better in the web-app arm, as assessed using standard quality of life questionnaires.

Moovcare works by having patients or their relatives report 12 symptoms weekly (for example,

asthenia, cough, dyspnea, anorexia, etc.) using a smartphone, tablet, or computer. An algorithm analyzes an association of symptoms and triggers email alerts to health care providers if relapse or dangerous medical conditions may be occurring. Providers follow up alerts by phone and schedule visits and imaging. “The sensitivity of the algorithm was high and was validated in two prospective studies,” Dr. Denis said. Sensitivity was 86%-100%.

Moovcare allowed earlier detection of relapse and improved overall survival for three reasons. “It allowed higher performance status at relapse, leading to more optimal therapy for relapsing patients. Dangerous medical conditions were detected earlier and treated earlier. It favored earlier supportive care, which improved quality of life. Less imaging was needed and performed at the right time,” Dr. Denis said.

Patients were monitored on a weekly basis, allowing more personalized care. The Moovcare web-app has been evaluated prospectively in about 300 patients, providing a high level of evidence of its utility in improving outcomes for patients with advanced lung cancer.

Press conference moderator Dr. Patricia Ganz commented that Moovcare is an example of a new way to improve the delivery of high-quality care to patients. “If we had a drug or some new intervention that caused this level of survival benefit, wouldn’t we want to go out and use it?” she asked. “This is a tremendous advance. This is personalized medicine. This is really tailoring it to the patient, and you can see how simple it is to collect this kind of data from the patient and then bring them in in between what would have been a scheduled visit.”

Dr. Ganz said the app overcomes putting off reporting symptoms until the next visit and reluctance to “bother the doctor.”

Another advantage of the app is that it alerts the health care team to potential problems and prompts them to “use tests when appropriate, not on a schedule, [which] leads to avoidance of waste in the follow-up of care of our patients,” she said.

Wedge resection beats SBRT for stage I lung cancer treatment

BY RICHARD PIZZI
Frontline Medical News

BALTIMORE – Surgical resection of early-stage non-small cell lung cancer afforded a superior survival advantage for patients than did stereotactic body radiation therapy (SBRT), based on study results presented at the 2016 annual meeting of the American Association for Thoracic Surgery.

While an increasing number of non-small cell lung cancer patients have been treated with SBRT, it appears that surgery may still be the better option.

“Frankly, I was surprised to see

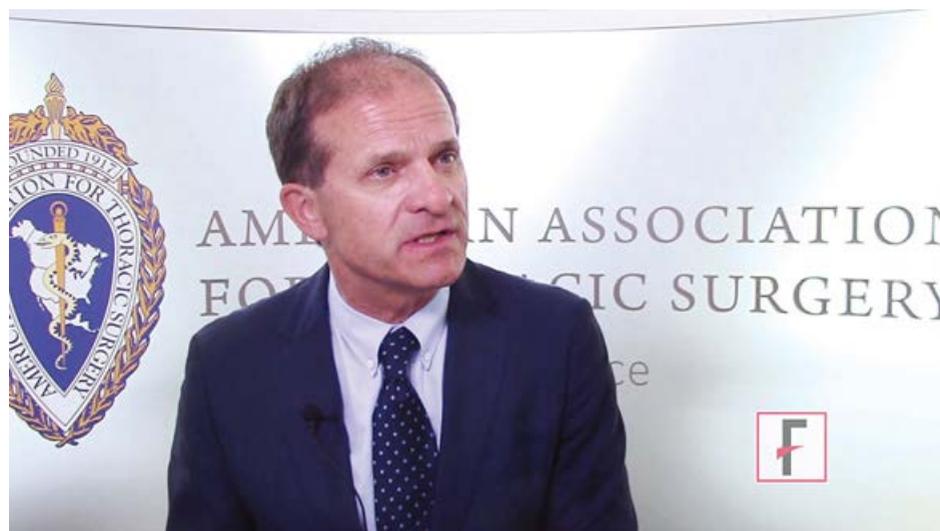
such a big difference between SBRT and wedge resection,” said Dr. Walter Weder, professor of surgery at University Hospital Zürich, in an interview at AATS 2016.

Dr. Weder served as a discussant on the paper, and said the results confirm that surgeons should be involved in discussions with patients when they are considering treatment options. “Surgery can be done safely... and patients should know this information,” he said.

Dr. Weder reported no relevant financial disclosures.

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To watch the interview, search “Weder” at www.chestphysician.org.

Palliation benefits extend to patients' caregivers

BY JESSICA CRAIG
Frontline Medical News

Introducing palliative care in combination with standard oncology care immediately following a cancer diagnosis results in improved quality of life and lower incidence of depression for caregivers of cancer patients.

"The integration of palliative care can improve patient care but the evidence is lacking about whether

"While patients receive a direct benefit from early palliative care, their caregivers experience a positive downstream effect, which may make it easier for them to care for their loved ones."

or not there are benefits [for] caregivers," Dr. Areej El-Jawahri of Massachusetts General Hospital, Boston, said in a presscast leading up to the annual meeting of the American Society of Clinical Oncology.

"This study suggests that early palliative care creates a powerful positive feedback loop in families facing cancer. While patients receive a direct benefit from early palliative care, their caregivers experience a positive downstream effect, which may make it easier for them to care for their

loved ones," she said.

Investigators enrolled 275 family caregivers of patients newly diagnosed with incurable lung or gastrointestinal cancers. Patients were randomly assigned to receive early

palliative care in addition to standard oncology care or to receive standard oncology care alone.

Palliative care involved a multifaceted team including nurses, social workers, and psychologists.

The palliative care intervention was patient focused.

Caregivers, who were defined as a relative or friend identified by the patient as the primary caregiver, were not required to attend palliative care



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SPIRIVA RESPIMAT—A DIFFERENT APPROACH ADDS NEW EXPECTATIONS FOR ASTHMA

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IMPORTANT SAFETY INFORMATION

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

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

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

VIEW ON THE NEWS

Dr. W. Michael Alberts, Master FCCP, comments: 'Early' palliative care (I prefer the term supportive care) has been shown to be of benefit to patients diagnosed with lung cancer. Proven benefit was welcome news to clinicians in the field who have now begun



to incorporate this treatment in many, if not most, patients. In addition to the patient, the caregivers may be adversely affected by the diagnosis of lung cancer and its treatment. It is great to see that the benefits of 'early' supportive care accrue to caregivers, as well as to the patient. This is one more reason to get supportive care involved early.



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appointments. However, about 50% of caregivers did attend, according to Dr. El-Jawahri.

At the time of enrollment and then at the time points of 12 and 14 weeks post enrollment, caregivers completed standard questionnaires. These included the 36-Item Short Form Health Survey and the Hospital Anx-

iety and Depression Scale. Both of these questionnaires assessed quality of life and mood.

Twelve weeks after the cancer diagnosis, those caregivers who received early palliative care reported experiencing significantly lower depression symptoms.

At the same time, their vitality and

social functioning had improved.

For patients who did not receive early palliative care, their caregivers' vitality and social functioning decreased.

"This is the first study showing a positive impact of a patient-focused palliative care intervention on family caregivers," said Dr. El-Jawahri.

The results of this study "really point out that we have so many ways to help our patients and their families," Dr. Julie Vose, president of ASCO, commented during the press-cast.

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

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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[®] RESPIMAT[®]**
(tiotropium bromide) INHALATION SPRAY

2015-2016 flu season milder than past 3 years

BY MICHELE G. SULLIVAN
Frontline Medical News

The 2015-2016 flu season was less severe than the last three seasons, with a lower hospi-

talization rate and fewer pediatric deaths.

Cases of influenza appeared later in the season than typically seen, and activity didn't peak until March, Stacy L. Davlin, Ph.D., wrote in Mor-

bidity and Mortality report (MMWR 2016; 22:567-75)

"During the most recent 18 influenza seasons, only two other seasons have peaked in March (2011-2012 and 2005-2006)," wrote Dr. Davlin, an

epidemiologist at the Centers for Disease Control and Prevention, Atlanta.

"Although summer influenza activity in the United States typically is low, influenza cases and outbreaks have occurred during summer

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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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 beta₂-agonist should be used. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, therapy with SPIRIVA RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT. **Paradoxical Bronchospasm:** Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta₂-agonist such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered. **Worsening of Narrow-Angle Glaucoma:** SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

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

widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. Since the same active ingredient (tiotropium bromide) is administered to COPD and asthma patients, prescribers and patients should take into account that the observed adverse reactions could be relevant for both patient populations independent of dosage strength.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: The SPIRIVA RESPIMAT clinical development program included ten placebo controlled clinical trials in COPD. Two trials were four-week 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 FEV₁ of 46%. In these 7 clinical trials, 68.3% of patients exposed to SPIRIVA RESPIMAT 5 mcg reported an adverse event compared to 68.7% of patients in the placebo group. There were 68 deaths in the SPIRIVA RESPIMAT 5 mcg treatment group (2.1%) and 52 deaths (1.6%) in patients who received placebo. The percentage of SPIRIVA RESPIMAT patients who discontinued due to an adverse event were 7.3% compared to 10% with placebo patients. The percentage of SPIRIVA RESPIMAT 5 mcg patients who experienced a serious adverse event were 15.0% compared to 15.1% with placebo patients. In both groups, the adverse event most commonly leading to discontinuation was COPD exacerbation (SPIRIVA RESPIMAT 2.0%, placebo 4.0%) which was also the most frequent serious adverse event. The most commonly reported adverse reactions were pharyngitis, cough, dry mouth, and sinusitis (Table 1). Other adverse reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, dysuria, and urinary retention.

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

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

*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT 5 mcg group at an incidence of 1% to 3% and at a higher incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo included: *Cardiac disorders:* palpitations; *Gastrointestinal disorders:* constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders:* dizziness; *Respiratory 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 (FEV₁) of 90.0% at baseline. Table 2 shows all adverse reactions that occurred with an incidence of >2% in the SPIRIVA RESPIMAT 2.5 mcg treatment group, and a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo.

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

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

*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT 2.5 mcg group at an incidence of 1% to 2% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo included: *Nervous system disorders:* dizziness; *Gastrointestinal disorders:* oropharyngeal, candidiasis, diarrhea; *Respiratory 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 FEV₁ of 98.3% at baseline. The adverse reaction profile for adolescent patients with asthma was comparable to that observed in adult patients with asthma. 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

months, and clinicians should remain vigilant in considering influenza in the differential diagnosis of summer respiratory illnesses,” Dr. Davlin said.

The most common influenza virus of the last season was A(H1N1), which accounted for about half of cases in those aged 5-24 years, and about 70% of cases in those younger

than 5 years and those 65 years and older.

Three novel viruses were seen as well: variants of A(H1N1), A(H1N2), and A(H3N2). The A(H1N1) variant occurred in a Minnesota resident who lived and worked in an area of swine farming, but who denied direct contact with pigs. The A(H3N2) vari-

ant occurred in a New Jersey resident who reported visiting a farm shortly before symptom onset. There was no evidence of human-to-human transmission. Both recovered fully without hospitalization. The A(H1N2) variant occurred in a Minnesota resident who was hospitalized but who recovered.

The CDC tested 2,408 viral specimens for susceptibility to antiviral medications. Among the 2,193 A(H1N1) specimens, less than 1% were resistant to oseltamivir and peramivir. All were susceptible to zanamivir. However, the testing found persistent high levels of A viruses resistant to amantadine and rimantadine.

Amantadine is not effective against B virus strains. Therefore, CDC does not recommend the use of amantadine as an anti-influenza medication.

Reports of influenza first exceeded the 2.1% baseline level in the week ending Dec. 26, 2015, and remained elevated for the next 17 weeks, with a peak of 3.6% of all outpatient visits

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/m² 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/m² 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/m² basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m² basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). **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

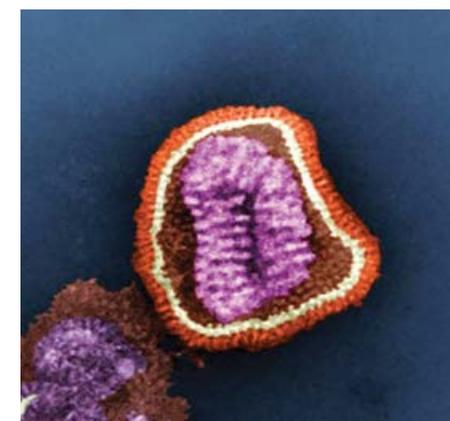
adolescent patients with asthma is warranted. The safety and efficacy of SPIRIVA RESPIMAT have not been established in pediatric patients less than 12 years of age.

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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Reports of influenza first exceeded 2.1% in the week ending Dec. 26, 2015, and peaked at 3.6% in the week ending March 12.

in the week ending March 12, according to the U.S. Outpatient Influenza-Like Illness Surveillance Network (ILINet).

Hospitalization rate for influenza-like illness was highest in those aged 65 years and older (85/100,000), and lowest in those aged 5-17 years (10/100,000). About 92% of adults hospitalized for flu-like illness had at least one underlying medical comorbidity, including obesity (42%), cardiovascular disease (40%), and metabolic disorders (38%). Almost half of children (48%) also had medical comorbidities, including asthma or other reactive airway disease (22%) and neurologic disorders (18%).

The percentage of deaths attributed to pneumonia and influenza peaked at 8% during the week ending March 19. The death rate in the last 5 years ranged from 9% in 2011-2012 to 11% in 2012-2013. Of this season's deaths, 74 occurred in children. There were 171 pediatric deaths in 2012-2013, 111 in 2013-2014, and 148 in 2014-2015.

As a CDC employee, Dr. Davlin had no financial disclosures.

Come for the day or make a weekend of it

1-Day Registration for CHEST 2016

If you'd like to attend CHEST Annual Meeting 2016 but have trouble scheduling time away from your practice, consider the 1-day registration. Register for any given day, Sunday through Wednesday. Or, attend for the weekend by registering for a postgraduate course on Saturday and 1 day on Sunday.

If you come for the weekend, consider bringing along your family. You won't be alone – there's so much for everyone to do in Los Angeles.

Postgraduate Courses

Saturday, Oct. 22

Attend a postgraduate course for an intensive learning experience. CME/CE credits and MOC points are available. Additional registration is required for all courses:

- Advanced Critical Care Echocardiography
- ICU Management: An Interactive Course for ICU Directors and Their Critical Care Team
- Lung Cancer: Update 2016
- Pulmonary Hypertension Interac-

tive Summit (InPHOCUS)

- Pulmonary Medicine 2016: Year in Review and Clinical Update
- Sleep Medicine 2016: Year in Review and Clinical Update
- 24th Annual Assembly of the American Association for Bronchology and Interventional Pulmonology

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Program Highlights

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and present from their respective perspective.

- **Problem-based learning sessions.** Study and discuss real clinical cases during small-group, interactive sessions designed to exercise your critical thinking skills.
- **Keynotes and honor lectures.** Attend our opening sessions to hear featured speakers discuss issues impacting chest medicine. And be sure to attend honor and memorial lectures, where chest medicine professionals will be recognized for their distinguished work.
- **Industry-supported sessions.** Don't miss these sessions focusing on current issues impacting the field.

Explore Los Angeles!

Los Angeles is known for its beautiful beaches, moderate temperatures, Hollywood glamour, and ritzy shopping. You'll enjoy the sunshine, moderate temperatures, and a bevy of sights and activities you can explore. Spend a few hours golfing, attend a TV show taping, shop on Rodeo Drive, or hike Runyon Canyon.

During your free time at CHEST 2016, you'll want to check out everything that Los Angeles has to offer.

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PRESIDENT'S REPORT: Location, location, location!

BY HEATHER M. NASH,
CMP, AND DR. BARBARA A.
PHILLIPS, MSPH, FCCP

Do you ever wonder how CHEST decides where to have its annual meeting? It's a science! We know that venue is an important consideration for busy clinicians who are trying to decide whether to invest time and money in attending a national meeting. Evaluation of criteria that determine the attractiveness of a given location for a national meeting is a job for professionals!

At CHEST, we are very fortunate to work with Heather Nash, CMP, who is the Senior Director, Meetings and Training Center Operations. She and her talented meetings team work together to choose a top-notch destination for the CHEST Annual Meeting.

The site selection for an annual meeting is a very important decision an association makes for its members. There is a variety of factors considered in making this decision, and the site selection process begins approximately 5-7 years in advance. Why so early, you might ask. The size of the CHEST Annual Meeting is the answer!

Our annual meeting requires a significant amount of meeting, exhibits, ballroom, and public foyer space. Additionally, the host city needs a minimum of 3,000 hotel rooms in the vicinity of the Convention Center. What this means is that the CHEST Annual Meeting does not fit into all convention centers and cities within the United States and Canada. Plus, other important criteria that are also considered are cost, travel, weather, and the amenities that a destination offers.

The site selection process starts with each destination's Convention and Visitors Bureau that is presented with a Request for Proposal, which includes a list of all the CHEST Annual Meeting specifications, requirements, and preferred dates. Based on those specifications, each city will compile a proposal of its full offerings, including meeting space, hotels, air and ground transportation, weather, cost, and key amenities of the destination. The puzzle that each city goes through is to determine whether the destination has all of the requirements needed by CHEST and to submit a complete proposal. It's fierce competition out there, which is why the process must start 5-7 years prior. The last step is to compile a site

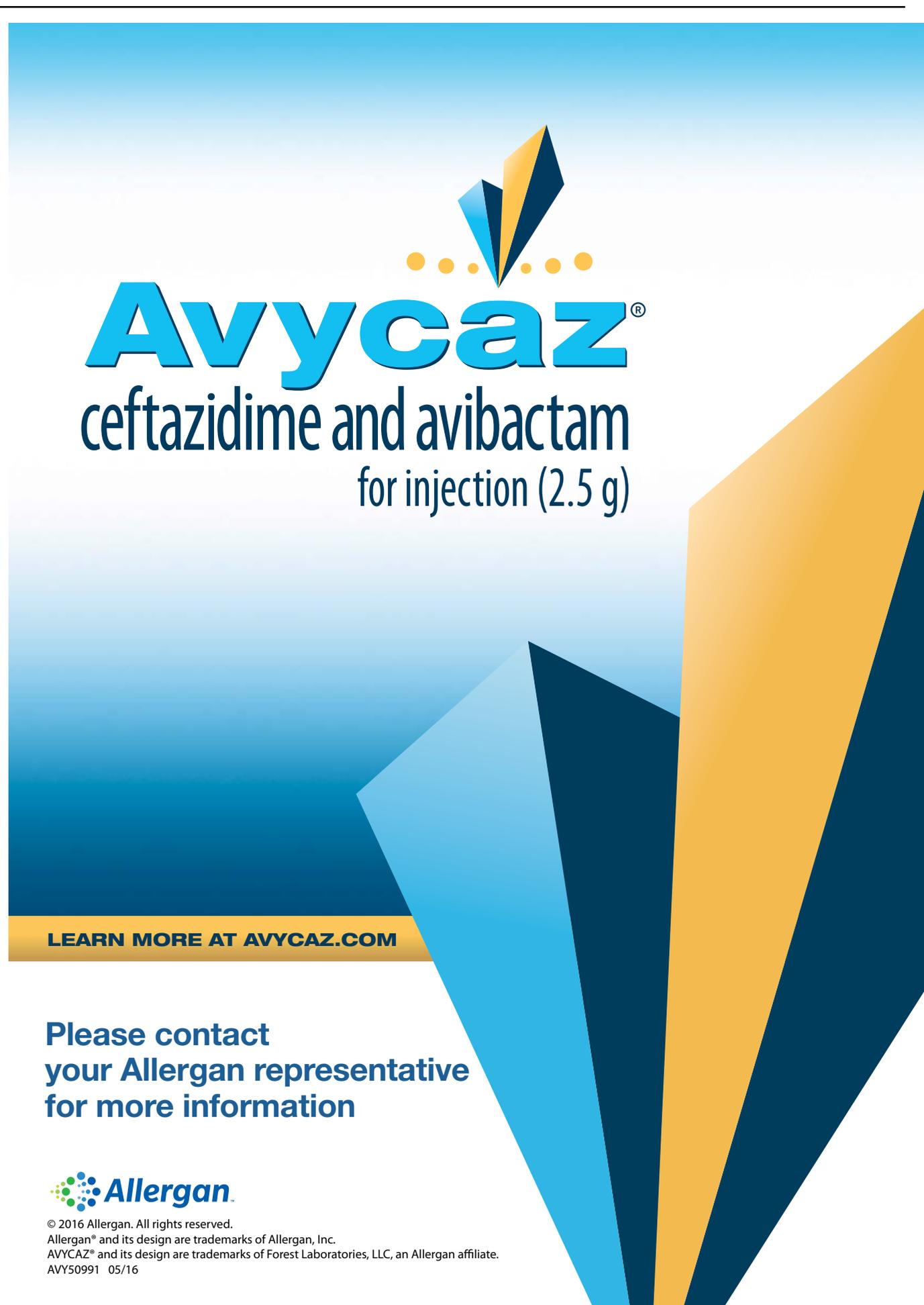
selection report that outlines, in order of priority, all components that CHEST needs to create a short list of locations and propose a final decision.

Why is the convention center

size so important? The CHEST Meeting Director must determine whether a certain venue and city can accommodate the CHEST Annual Meeting. A few key factors that are reviewed include exhibit space; a

minimum of 300,000+ gross square feet, 30+ flexible size meeting rooms that can accommodate 75-400 people each for educational sessions, opening keynote session space for

Continued on following page



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Continued from previous page

2,500 people, a Simulation Center space, not to mention the additional needs for registration, self-study stations, games, and other e-learning opportunities.

Many times, the cities with the larger convention centers attract CHEST (Chicago, New Orleans, Toronto, San Francisco, and Los Angeles). However, CHEST has had some of its strongest attendance in cities with somewhat smaller convention centers (Montreal, Austin, Honolulu, and Vancouver).

Of course, there are the other aspects of an annual meeting that are very important to clinicians, guests, and attendees. How easy is it to get a flight at a reasonable cost? How close are the hotels and what are the room rates of the official meeting hotels? Can I walk to the convention center or do we need to get on a bus? Can I walk to a restaurant after a full day of sessions? These are just a few questions we receive often by our CHEST Help Team representatives. We track these types of questions so that when we engage a prospective destination, these questions are answered in the final proposal and site selection report.

The CHEST Annual Meeting

2016 will be held in Los Angeles, California. Los Angeles was confirmed as the location in 2011, based upon the improved infrastructure in the downtown Los Angeles area and the renovations made within the Los Angeles Convention Center.

The infrastructure mentioned is an area called L.A. LIVE, which is

the sports and entertainment district that surrounds the STAPLES Center and Microsoft Theater, JW Marriott, and the Los Angeles Convention Center. The campus features sports and music venues, nightclubs, restaurants, a bowling alley, the GRAMMY museum, and movie theaters. L.A. LIVE is the premier

destination for live entertainment in downtown Los Angeles and very walkable!

We hope you have learned a bit about the process we adhere to in the site selection process for the CHEST Annual Meeting, and we look forward to welcoming you in October.

See you in Los Angeles!

CHEST Leadership Attends Conference in Rome



Dr. Francesco de Blasio, FCCP, Chair of the CHEST Council of Global Governors; is shown here with Dr. Barbara Phillips, FCCP, CHEST President. They attended the International Conference on Respiratory Pathophysiology, Sleep, and Breathing in Rome, Italy, as members of the Scientific Committee.

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	Pulmonary Medicine Board Review August 24-28

Attend optional sessions August 23:

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Details available at boardreview.chestnet.org.

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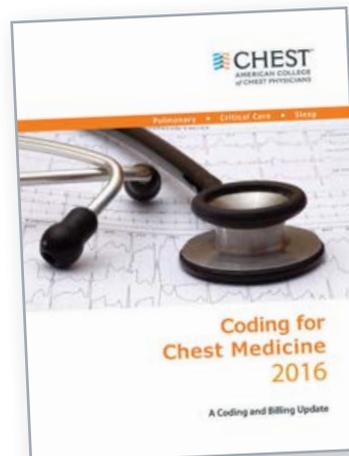
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CHEST Foundation: Training village doctors in China

In 2012, Dr. Renli Qiao, FCCP, won the D. Robert McCaffree, MD, Master FCCP Humanitarian Award for his critical work with village doctors in rural China. Because medical schools in China are located in larger metropolitan areas where graduates are likely to stay, medical resources are unevenly distributed across the country. Physicians with shortened medical education



often staff rural hospitals, and smaller villages usually house a single village doctor with a high-school diploma and 3-6 months of medical training.

Inspired by his work with the China California Heart Watch (CCHW), Dr. Qiao created a program to train rural medical professionals so that their efforts would have a sustaining impact on the care that residents of these villages receive. Volunteer physicians traveled through as many

villages on foot to spend several days in each village where they would see about 250 villagers a day. In these villages, the doctors were also able to perform heart examinations for hundreds of children in the village schools. The team observed that although hypertension is the leading cause of death in China and the antihypertensive drugs are relatively affordable, there is a high incidence of hypertension, and up to 95% of patients with hypertension were never diagnosed or treated.

Realizing the need to train doctors on the importance of preventive care, early diagnoses, and treatment of hypertension, Dr. Qiao led the initiative to educate thousands of doctors in the Yunnan province. His model involved 2-day seminars and included participatory workshops, lectures, group collaboration, and the dissection of clinical cases. Dr. Qiao's effort not only improved the lives of thousands of patients but also achieved a lasting model to educate rural doctors. He is now aiding in the China-CHEST PCCM program efforts to establish PCCM as a subspecialty in China.



Dr. Qiao helping a patient in rural China.

CHEST Past President honored

The Lung Association of Saskatchewan has conferred its highest award on Dr. Darcy Marciniuk, FCCP. The Lifetime Achievement Award recognizes 25 years of outstanding service by Dr. Marciniuk to improving respiratory health in Saskatchewan. Dr. Marciniuk is currently associate vice president of research (Acting) at the University of Saskatchewan, Canada, in addition to continuing to serve as professor of medicine in the division of respiratory, critical care, and sleep medicine.

Dr. Marciniuk led the development of both respiratory services and chronic disease management in general in the Saskatoon Health Region, which is now spreading to the province as a whole. He began the LiveWell program that started with respiratory health and was used as a model to expand the chronic disease management program to other health areas. He was a leader in the development of the Lung Health Institute and is currently spearheading the establishment of a respiratory research center at the University of Saskatchewan. He has done extensive research in the area of chronic ob-

structive pulmonary disease, for which he is nationally and internationally recognized with more than 100 peer-reviewed publications. Dr. Marciniuk is currently a leader in the CHEST initiative to develop a national respiratory training program in China, which is being implemented in collaboration with the Chinese government.

CHEST congratulates Dr. Marciniuk on this prestigious honor.



Ms. Pat Smith, Chair of the Lung Association of Saskatchewan volunteer board, presents the 2016 Lifetime Achievement Award to Dr. Darcy Marciniuk at the Respirology State of the Art Conference, Saskatoon, May 28, 2016.

This month in CHEST: Editor's picks

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

EDITORIAL

Burnout syndrome in ICU caregivers: Time to extinguish! By Dr. S. Pastores, FCCP

COMMENTARY

An Official Critical Care Societies Collaborative Statement – Burnout syndrome in critical care health-care professionals: A call for action. By Dr. M. Moss et al.

GIANTS IN CHEST MEDICINE

Neil R. MacIntyre, MD, FCCP. By Dr. Lisa K. Moores, FCCP

ORIGINAL RESEARCH

Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome. By Dr. J. R. Masa et al.

Treprostinil administered to treat pulmonary arterial hypertension using a fully implantable programmable intravascular delivery system: Results of the DeliVey for PAH Trial. By Dr. R. C. Bourge et al.

Improving quality of acute asthma care in US hospitals: Changes between 1999-2000 and 2012-2013. By Dr. K. Hasegawa et al.



NUCALA

THE FIRST TARGETED ANTI-INTERLEUKIN 5 THERAPY FOR SEVERE ASTHMA WITH AN EOSINOPHILIC PHENOTYPE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype.

- ✓ NUCALA is not indicated for treatment of other eosinophilic conditions.
- ✓ NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.



Important Safety Information

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration but in some instances can have a delayed onset (ie, days). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms, acute exacerbations, or acute bronchospasm.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared to none in placebo. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

It is unknown if NUCALA will influence a patient's response against parasites. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS

The most common adverse reactions ($\geq 3\%$ and more common than placebo) reported in the first 24 weeks of 2 clinical trials with NUCALA (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasm, 3% (<1%).

NUCALA IS PROVEN TO:

- ✓ **Reduce exacerbations* by 53%** (NUCALA: 0.83/year; placebo: 1.74/year, $P < 0.001$)¹
- ✓ **Reduce daily OCS dose while maintaining asthma control** ($P = 0.008$)¹
- ✓ **Improve quality of life (SGRQ) with a responder rate of 71% for NUCALA compared with 55% for placebo** (odds ratio of 2.1; 95% CI: 1.3, 3.2)[†]
 - Statistical hierarchy was not met, endpoint is exploratory, and results are descriptive only¹

In a 32-week study of patients with severe asthma with an eosinophilic phenotype, NUCALA (n=194) and placebo (n=191), each added to high-dose ICS and at least 1 other controller with or without OCS and dosed once every 4 weeks, were compared to evaluate the frequency of exacerbations. In a 24-week study of 135 patients with severe asthma with an eosinophilic phenotype, NUCALA and placebo were each added to high-dose ICS and at least 1 other controller and dosed once every 4 weeks to compare the percent reduction in daily OCS dose (weeks 20 to 24) while maintaining asthma control.¹

ICS=inhaled corticosteroids; OCS=oral corticosteroids; SGRQ=St. George's Respiratory Questionnaire.

*Defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients requiring maintenance oral/systemic corticosteroids, exacerbations were defined as at least double the existing maintenance dose for at least 3 days.¹

[†]The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response is defined as a change in score of 4 or more as threshold.¹

Visit NUCALAhcp.com for more information, including patient access programs.

Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, 10% of subjects who received NUCALA experienced systemic (allergic and nonallergic) and local site reactions compared to 7% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of subjects who received NUCALA compared to 2% of subjects in the placebo group. Manifestations included rash, pruritus, headache, and myalgia. Systemic nonallergic reactions were reported by 2% of subjects who received NUCALA and 3% of subjects in the placebo group. Manifestations included rash, flushing, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (eg, pain, erythema, swelling, itching, and burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothersbaby.org/asthma.

The data on pregnancy exposures from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are progressively transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy.

Reference: 1. Data on file, GSK.

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

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Nucala[®]
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA®

(mepolizumab) for injection, for subcutaneous use

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

INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. [See Clinical Studies of full Prescribing Information.]

Limitations of Use

- NUCALA is not indicated for treatment of other eosinophilic conditions.
- NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued [see Contraindications].

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [see Adverse Reactions]. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions [see Warnings and Precautions]
- Opportunistic infections: herpes zoster [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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation [see Clinical Studies of full Prescribing Information]. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) and local site reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety

Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

Immunogenicity

Overall, 15/260 (6%) subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothersbaby.org/asthma.

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was

no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC [see Data].

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryo-fetal development of IL-5-deficient mice has been reported to be generally unaffected relative to wild-type mice.

Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see Use in Specific Populations]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. [See Clinical Studies of full Prescribing Information.] Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies [see Adverse Reactions].

Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 38) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

OVERDOSAGE

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients varicella vaccination should be considered before starting treatment with NUCALA.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothersbaby.org/asthma [see Use in Specific Populations].

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NETWORKS: ACOS, airway clearance therapies, early mobilization

Airways Disorders

The asthma COPD overlap syndrome: hype or reality?

In 2014, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) published a joint document on the asthma COPD overlap syndrome (ACOS). While the concept of ACOS is not new, it remains highly debated since its introduction in 1961. ACOS is characterized by persistent airflow limitation with features that are shared with both asthma and COPD. For example, younger asthmatics may develop persistent expiratory airflow limitation from airway remodeling or smoking.

Alternatively, patients with COPD may have concurrent features of atopy. Prevalence of ACOS is estimated at 20% in those with obstructive airway disease (Gibson. *Thorax*. 2015;70[7]:683). Data from the COP-

DGene cohort suggest that patients with ACOS have more frequent and severe respiratory exacerbations, less emphysema, and greater airway wall thickness (Hardin. *Eur Respir J*. 2014;44[2]:341).

Studies evaluating differences in response to therapy are needed to make ACOS more relevant to the practicing clinician.

The mechanisms behind ACOS remain poorly understood. Gelb and colleagues recently reported their observations of loss of lung elastic recoil and presence of centrilobular emphysema in a subset of nonsmokers with chronic asthma and persistent expiratory airflow limitation (*Chest*. 2015; 148[2]:313; *J Allergy Clin Immunol*. 2015;136[3]:553). In two COPD cohorts, Christenson and colleagues found that asthma-associated gene signatures were associated with increased disease severity, eosinophil counts, bronchodilator reversibility, and ICS response (*Am J Respir Crit Care Med*. 2015;191[7]:758).

Data presented recently from Spiromics COPD and SARP severe asthma cohorts suggest that subjects with ACOS share a phenotype that falls between COPD and asthma. Allele frequency of candidate genes associated with smoking behavior and allergy in ACOS was intermediate between COPD and asthma (Li et al. *Am J Respir Crit Care Med*. 2016;A6237).

As with asthma and COPD, there exists significant heterogeneity within ACOS. Despite its high prevalence, evidence on how to consistently identify and best manage this group of patients is lacking. This is in part due to large clinical studies excluding patients with asthma COPD overlap. Additional research will help better understand the different phenotypes and endotypes of ACOS.

Real life pragmatic studies evaluating differences in response to therapy are needed to make ACOS more relevant to the practicing clinician.

Dr. Sandhya Khurana, FCCP
Vice-Chair

improving these outcomes and optimizing recovery after acute illnesses (Kim et al. *Chest*. 2011;140[3]:626).

Despite this knowledge, the study of simple ACTs has been largely overlooked for decades. Many of the treatments we currently use, such as positive expiratory pressure devices (for example, the Acapella device), percussive vests, and intrapulmonary percussive ventilation, have few

The study of simple ACTs has been largely overlooked for decades. Many of the treatments we currently use ... have few studies to support their efficacy.

studies to support their efficacy, with the ones that exist having very small sample sizes and show no superiority to simple manual techniques (Flume et al. *Respir Care*. 2009; 54[4]:522).

As I walk by a patient's room and see a respiratory therapist clapping on a patient's back, I reflect on the fact that research on ACTs has essentially been at a standstill, and we continue to rely on therapies that are no better than the ones used in the 1800s.

Our institution has established an Airway Clearance Research Group and has already conducted several bench studies evaluating some of these airway clearance therapies, with goals to develop novel techniques and to start clinical trials, with collaboration from this research steering committee.

We hope that furthering the study of ACTs, and determining which therapies are most effective under different clinical settings, will not only improve clinical outcomes in chronic conditions such as bronchiectasis but also improve outcomes after pneumonia, strokes, thoracic surgeries, and during mechanical

Continued on page 51



DR. KHURANA

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Clinical Research

Airway clearance therapies

Many acute and chronic respiratory conditions, such as pneumonia and bronchiectasis, are not only associated with an increase in the quantity and viscosity of respiratory secretions but also with impaired ciliary function and cough, with the latter being very common during mechanical ventilation and after strokes or thoracic surgical procedures. Retention of these secretions are associated with poor patient outcomes, and airway clearance therapies (ACT) are key to



DR. AMALAKUHAN

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CHICAGO

Mount Sinai—Four member pulmonary/critical care group in Chicago seeks 5th.

Based in large urban teaching hospital with pulmonary fellowship program, Division part of large multi-specialty hospital affiliated group.

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Contact Joseph Rosman, MD
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* * * * *

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We're seeking a dynamic and accomplished young physician with a passion for medicine, good interpersonal skills, a willingness to challenge herself/himself and us, and a desire to work collegially and collaboratively within a group.

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PULMONARY / CRITICAL CARE / SLEEP MEDICINE – PORTLAND, MAINE

Chest Medicine Associates is a well-respected, established, 16 physician single specialty, private practice group in Portland, Maine. We seek pulmonary/critical care/sleep medicine physicians to expand our services. We have a strong partnership with Maine Medical Center, the state's largest tertiary care and teaching hospital, to provide 24/7 medical and neurological critical care and consultative pulmonary medicine services.

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FRONTLINE
 MEDICAL COMMUNICATIONS

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ventilation, where airway clearance is key. Something so simple has the potential to impact a wide population of patients.

Dr. Bravein Amalakuhan
Fellow-in-Training Member

Critical Care

Early mobilization of the critically ill patient

Deconditioning is a well known complication of prolonged ICU stays. It is



DR. NARASIMHAN

a factor in long-term mechanical ventilation and contributes to an increased length of stay and comorbidities. The severity of illness, presence of invasive catheters, and the need for sedation

in order to provide adequate ventilation are risk factors for immobility. Critically ill patients who are not mobilized experience a decreased quality of life (Needham. *JAMA*. 2008;300:1685).

The changes seen have been shown to persist up to a year after discharge, with a mean loss of 18% body weight, a 5% loss of muscle strength, and a decreased 6-minute walk distance (Herridge et al. *N Engl J Med*. 2003;348[8]:683; Herridge. *Crit Care Med*. 2009;37:S457).

There are many safety concerns when mobilizing critically ill patients, but studies have shown that early mobilization is safe with less than 1% of patients having adverse events such as falling, tube removal, and

blood pressure instability (Bailey et al. *Crit Care Med*. 2007;35[1]:139). Barriers to mobilization include ICU staffing, deep sedation, ICU culture, and resources. Adherence to therapy is improved with the use of protocols.

These should include automated

Decreases in ICU and hospital lengths of stay, time supported by mechanical ventilation, and cost reductions have been shown with mobilization.

awakening trials and spontaneous breathing trials that allow for decreases in sedation and, therefore, improvement in mobilization performance (Drolet et al. *Phys Ther*. 2013;93[2]:197).

Early mobilization improves mortality and decreases morbidity. Safe protocols to implement early mobilization have been developed around the country. Decreases in ICU and hospital lengths of stay, time supported by mechanical ventilation, and cost reduction have been shown with mobilization in multiple studies. A multidisciplinary team approach and a change in ICU culture will help to accomplish this important initiative.

Dr. Mangala Narasimhan, FCCP
Steering Committee Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Caregivers and training for kids receiving chronic home invasive ventilation

Despite years of experience in discharging pediatric patients receiving chronic home invasive ventilation, their mortality rate remains high, ranging from 21% to 27.5% with unscheduled readmission at 40% (Boroughs et al. *Home Health Nurse*. 2012;30:103)



MS. KUN

to 21% (Edwards et al. *J Pediatr*. 2010;157[6]:955; Kun et al. *Pediatr Pulmonol*. 2012;47[4]:409). While

there were major improvements in technology and newer ventilators, and better community resources, the one key component of our HMV program remains the same – the caregivers. It is a frightening experience for every family to hear that their child needs ventilator support: every discharge is a daunting task and a life-changing experience.

It seems logical to postulate that we might have improved mortality/readmission outcomes if we have competent caregivers.

Recent ATS guidelines recommend that “an awake, trained caregiver should be present at all times, and at least two family caregivers should be trained specifically for the child’s care” (*Am J Respir Crit Care Med*. 2016;193[8]:e16).

The need to shore up on emergency care in the home is further supported when we review studies examining pediatric emergency home ventilation practices for both families and licensed home health nurses (Kun et al. *Pediatr Pulmonol*. 2010;45[3]:270; Kun. *Pediatr Pulmonol*. 2015;50[7]:691).

Understanding and responding to ventilator alarms remain a major challenge for caregivers and home health nurses. Future directions where we can help our caregivers and families improve home emergency care training include simulation video and using the technology of hand-held devices.

Sheila Kun, RN, BSN
Steering Committee Member

Interstitial and Diffuse Lung Disease

New clinic consortium offers help to patients with rare lung diseases

On the heels of the success of the LAM Foundation’s research and clinic networks, several patient advocacy



DR. DILLING

groups for rare lung diseases approached the LAM Foundation about incorporating the care of other rare lung diseases into the same clinic network. In 2015, the Rare Lung Diseases Consortium was established. It represents a unique collaboration of these patient advocacy groups, the National Institutes of Health,

and clinical investigators. It hopes to utilize the Rare Lung Disease Clinic Network as a resource in understanding the clinical course of several rare lung diseases and as a vehicle to initiate funded clinical

The first Rare Lung Diseases Consortium Conference is scheduled for September 22-25, 2016, in Cincinnati.

trials in patients under the care of clinical investigators working at those various sites.

There are currently 29 geographically distributed Rare Lung Disease Clinic Network clinics in the United States, and another 18 clinics distributed internationally. The clinic directors have held two organizational meetings, including the most recent one in May 2016. The initial three research projects, “National Pulmonary Alveolar Proteinosis Registry,” “A Longitudinal Study of Hermansky-Pudlak Syndrome,” and “Multicenter International Durability and Safety of Sirolimus in LAM Trial (MIDAS),” are noninterventional longitudinal disease observational studies.

The first Rare Lung Diseases Consortium Conference is scheduled for September 22-25, 2016, in Cincinnati. It will be a combined educational and research conference, with attendance from clinicians, scientists, patient advocacy organizations, and patients with their families.

More information, including a list of the 22 diseases initially designated for care and study in the network and a map of all of the clinic network sites, is available at <https://www.rarediseasesnetwork.org/cms/rld/>.

Dr. Daniel F. Dilling, FCCP
Steering Committee Member

In Memoriam

CHEST has been informed of the following members’ deaths. We extend our sincere condolences.

Vincent C. Manganiello, MD, PhD, died January 2016.

Lawrence H. Cohn, MD, FCCP – Past President, died January 9, 2016.

Suzanne K. Wedel, MD, FCCP, died March 2016.

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