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Blood pressure-lowering therapy is an important treatment for patients with sleep apnea, according to researchers.

PAP doesn't cut rates of cardiovascular events, death

BY MARY ANN MOON
Frontline Medical News

Positive airway pressure, whether delivered continuously (CPAP) or as adaptive servoventilation, doesn't reduce the rate of cardiovascular (CV) events or death in patients who have sleep apnea, according to a report published online July 11 in JAMA.

Positive airway pressure (PAP) relieves the symptoms of sleep apnea and has been reported to improve cardiovascular risk factors such as hypertension, insulin resistance, and endothelial dysfunction. However, whether the treatment improves "hard" vascular outcomes such as stroke and MI has never been established, said

Jie Yu, MD, of the department of cardiology, Peking University and the Ministries of Health and Education, Beijing, and his associates.

They performed a systematic review of the literature and a meta-analysis of 10 randomized clinical trials that compared PAP against standard care or a sham treatment and had at least 6 months of follow-up for CV events. The meta-analysis involved 7,266 participants who had either obstructive (5,683 patients) or central (1,583 patients) sleep apnea. There were 356 major adverse CV events and 613 deaths during a median follow-up of 6-68 months.

The use of PAP showed no significant association with a range of outcomes: major adverse CV PAP DIDN'T IMPROVE BLOOD PRESSURE // *continued on page 7*

Azithromycin improves QOL in asthmatics

Drug cut exacerbations

BY DOUG BRUNK
Frontline Medical News

Adults with persistent symptomatic asthma who took azithromycin as an add-on therapy experienced fewer exacerbations and had improved quality of life, compared with their peers who took a placebo, a multicenter, randomized trial demonstrated.

"Macrolide antibiotics have antibacterial, antiviral, and anti-inflammatory effects, and are reported to be beneficial in both eosinophilic and noneosinophilic subtypes," a group of Australian researchers wrote online July 4 in *The Lancet* (doi: org/10.1016/S0140-6736[17]31281-3). "Systematic reviews of randomized, controlled trials report benefits of macrolides on asthma symptoms but [we] are unable to draw conclusions about the effects on other endpoints, including exacerbations, due to lack of data, heterogeneity of results, and inadequate study design and sample size."

Led by Peter G. Gibson, MBBS, of Hunter Medical Research Institute, New South Wales, Australia, researchers at eight clinical sites conducted ADD-ON THERAPY CUTS EXACERBATIONS // *continued on page 4*

INSIDE HIGHLIGHT

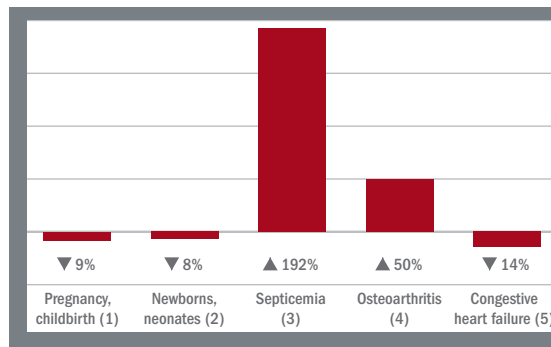
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Reasons for inpatient stays shift

The reasons for inpatient stays have shifted. See 2014's most frequent diagnoses for hospital stays, following pregnancy/childbirth and newborns and neonates, on page 7.

HELP PRESERVE MORE LUNG FUNCTION

Reduce lung function decline with Esbriet¹⁻⁴

BROAD PATIENT POPULATION



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

DEMONSTRATED EFFICACY



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

IPF=idiopathic pulmonary fibrosis.

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

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

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

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

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

Indication

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

Select Important Safety Information

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

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

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

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

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

**WORLDWIDE
PATIENT
EXPERIENCE**



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

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

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

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

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

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

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

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

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

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

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

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

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

ducted a randomized trial to test the hypothesis that the macrolide antibiotic azithromycin reduces asthma exacerbations and improves quality of life in patients with symptomatic asthma on inhaled maintenance therapy. To be eligible for the trial, known as Asthma and Macrolides:

the Azithromycin Efficacy and Safety Study, or AMAZES, patients had to be at least 18 years of age, be using an inhaled corticosteroid and long-acting bronchodilator, and have no hearing impairment or abnormal prolongation of the corrected QT interval. Primary efficacy

endpoints were the total number of asthma exacerbations (severe and moderate) over 48 weeks and asthma quality of life based on responses to the Asthma Quality of Life Questionnaire (Chest. 1999 May;115[5]:1265-70). Of the 420 patients, 213 were allocated to take

500 mg azithromycin three times weekly and 207 were allocated to placebo. In all, 168 patients in the azithromycin group completed 48 weeks of treatment, compared with 166 in the placebo group. Their median age was 60 years, 76% had

Continued on page 7



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

5.2 Photosensitivity Reaction or Rash

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

5.3 Gastrointestinal Disorders

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials. ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials

ESBRIET® (pirfenidone)

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

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

Strong CYP1A2 Inhibitors

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

VIEW ON THE NEWS

The impact on community microbial resistance remains unclear

Since microbial resistance is a well known side effect of antibiotic use, add-on therapy with azithromycin in asthma needs

to be restricted to those patients with the highest unmet medical need (for example, frequent exacerbators) and to time periods with the greatest risk of exacerbations (such as winter). Biomarkers that predict the

therapeutic response to macrolides might facilitate optimal patient selection. Further research is needed to elucidate the most important mechanism of action of these pleiotropic drugs. Macrolides have anti-inflammatory,

antibacterial, and antiviral effects. However, the authors did not observe a reduction in inflammatory cell counts in sputum to support a definite anti-inflammatory effect. Azithromycin also was effective in patients with and without potentially pathogenic microorganisms in sputum cultures at baseline. Since azithromycin reduced both asthma exacerbations and respiratory infections, the benefits of azithromycin might be caused by preventing viral-induced attacks in asthma. Azithromycin stimulates phagocytosis of microbes and dead cells by macrophages (i.e., efferocytosis), an effect that is likely to be independent of the nature of the accompanying neutrophilic or eosinophilic airway inflammation.

Dr. Gibson and his colleagues have clearly shown that add-on therapy with azithromycin is effective and safe in adult patients with uncontrolled asthma despite treatment with inhaled corticosteroids and long-acting beta-agonists. Azithromycin benefited patients with both eosinophilic and noneosinophilic asthma. However, the effects of long-term therapy with macrolides on community microbial resistance remain a public health concern. Future studies with potentially safer nonantibiotic macrolides in uncontrolled severe asthma are warranted. Since the antimicrobial effects probably contribute to the overall efficacy of macrolides, the beneficial effects of nonantibiotic macrolides might be intermediate between macrolide antibiotics and placebo.

This text is excerpted from a commentary published online July 4 in The Lancet (doi.org/10.1016/S0140-6736[17]31547-7). Guy Brusselle, MD, is with the department of respiratory medicine at Ghent (Belgium) University Hospital and Ian Pavord, MD, is with the University of Oxford's Nuffield Department of Medicine, in England. Both authors disclosed having received honoraria and other financial support from numerous pharmaceutical companies.

ESBRIET® (pirfenidone)

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

Moderate CYP1A2 Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

7.2 CYP1A2 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

ESBRIET® (pirfenidone)

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

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

8.7 Renal Impairment

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

8.8 Smokers

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

10 OVERDOSAGE

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

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

17 PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Events

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

Smokers

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

Take with Food

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

Distributed by:
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Frequent bronchiectasis exacerbations linked to higher mortality

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – Bronchiectasis patients with three or more exacerbations per year had twice the mortality during 5-year follow-up as patients with no recent exacerbations, in a prospective registry of nearly 2,600 European bronchiectasis patients.

A multivariate analysis showed this statistically significant doubled death rate after adjustment for baseline demographic and clinical differences between patients

with no exacerbations during the year before they entered the registry, James D. Chalmers, MD, said at an international conference of the American Thoracic Society.



DR. CHALMERS

Having had frequent exacerbations at a rate of three or more annually prior to enrollment was common, with 37% of the 2,596 bronchiectasis patients in the registry having this history, said Dr. Chalmers, a pulmonologist at the University of Dundee, Scotland. This 37% prevalence contrasted with a 19% U.S. prevalence of bronchiectasis patients having two or more exacerbations per year among 2,114 patients enrolled in a 13-center U.S. registry that was reported during the same session by Timothy R. Aksamit, MD, a pulmonologist at the Mayo Clinic in Rochester, Minn. Dr. Aksamit contended that the U.S. registry tried to exclusively enroll patients with bronchiectasis and no other disorder, possibly explaining the prevalence difference between Europe and the United States.

The European registry included

patients with bronchiectasis seen in 10 centers in seven European countries and Israel. They averaged 67 years of age. While more than a third had a history of at least three exacerbations a year, one-quarter had no exacerbations during the year before they entered the study.

The prospective study also showed that, among patients with three or more exacerbations annually, the risk for a subsequent exacerbation was five times higher than among patients with no recent exacerbations.

The U.S. registry reported by Dr. Aksamit had 2-year follow-up data for 1,049 of the enrolled patients, a subgroup that closely matched the entire population initially enrolled. The



DR. AKSAMIT

2-year follow-up showed an overall average exacerbation rate of 0.75 episodes per year, but this was driven largely by the subgroup of patients who entered the registry with a history of two or more exacerbations per year, who then averaged about 2.6 exacerbations during follow-up. In contrast, patients who entered the registry with a history of fewer than two exacerbations per year averaged fewer than a third of an exacerbation per year during follow-up.

The European bronchiectasis registry was partially funded by Bayer. Dr. Chalmers has been a consultant to Bayer and to AstraZeneca, Basilea, Grifols, Napp, and Raptor and has received research funding from Aradigm, AstraZeneca, Bayer, GlaxoSmithKline, and Pfizer.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: The longitudinal outcomes of patients within both of these bronchiectasis cohorts demonstrate that there is a subset of patients with this condition who are prone to exacerbation and that this high exacerbation rate portends a very poor prognosis. As such, increased focus should be placed on this particular group of patients in an attempt to prevent exacerbations and subsequent clinical decline.



CRITICAL CARE COMMENTARY

Medical students: The role of conscience in medicine. // 41

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Septicemia admissions almost tripled from 2005 to 2014

BY RICHARD FRANKI

Frontline Medical News

Admissions for septicemia nearly tripled from 2005 to 2014, as it became the third most common diagnosis for hospital stays, according to the Agency for Healthcare Research and Quality.

There were more than 1.5 million hospital stays with a principal diagnosis of septicemia in 2014, an increase of 192% over the 518,000 stays in 2005. The only diagnoses with more admissions in 2014 were pregnancy/childbirth with 4.1 million stays and newborns/neonates at almost 4 million, although both were down from 2005. That year, septicemia did not even rank among the top 10 diagnoses, the AHRQ reported.

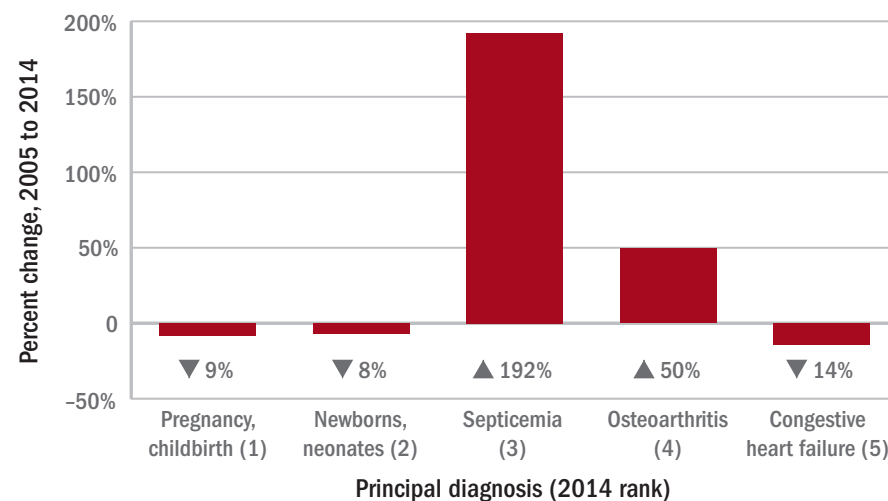
Osteoarthritis was the fourth most common diagnosis in 2014 with almost 1.1 million stays, an increase of almost 50% from 2004, when it was the seventh most common diagnosis. Admissions for the fifth most common diagnosis in 2014, congestive heart failure, were down by over 14% from 2005, data from the National Inpatient Sample show.

Pneumonia, which was the third most common diagnosis in 2005, dropped by 32% and ended up in sixth place in 2014, while admissions for coronary atherosclerosis, which was fourth in 2005, decreased by 63%, dropping out of the top 10, by 2014, the AHRQ said.

Septicemia was the most common diagnosis for inpatient stays among those aged 75 years and older and

FIVE MOST COMMON DIAGNOSES FOR INPATIENT STAYS, 2014

Change in the number of admissions from 2005 to 2014



Note: Based on data from the National Inpatient Sample.

Source: Agency for Healthcare Research and Quality

the second most common for those aged 65-74 and 45-64. The leading nonmaternal, non-neonatal diagnosis in the two youngest age groups, 0-17 and 18-44 years, was mood dis-

orders, and the most common cause of admissions for those aged 45-64 and 65-74 years was osteoarthritis, the AHRQ reported.

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PAP didn't improve blood pressure // continued from page 1

events (relative risk, 0.77; $P = .19$), major adverse CV events plus hospitalization for unstable angina (RR, 0.92; $P = .54$), cardiovascular death (RR, 1.15; $P = .30$), all-cause mortality (RR, 1.13; $P = .08$), noncardiovascular death (RR, 0.85; $P = .33$), acute coronary syndromes (RR, 1.00; $P = .99$), stroke (RR, 0.90; $P = .47$), and heart failure (RR, 1.03; $P = .60$). This lack of treatment benefit persisted regardless of length of follow-up, adherence to treatment, or baseline score on the apnea-hypopnea index, the investigators said (JAMA. 2017 Jul 11. doi: 10.1001/jama.2017.7967).

PAP also failed to improve blood pressure, body mass index, any lipid parameter, glycemia, or quality-of-life scores on the EQ-5D. It did improve sleepiness and some measures of physical and mental well-being.

"The evidence from these [randomized

clinical trials] suggests that the association [between] sleep apnea and vascular outcomes and death ... may represent disease processes that cannot be ameliorated by PAP delivered at the average intensity achieved in these clinical trials or by currently feasible methods in clinical practice," Dr. Yu and his associates said.

Their findings also "emphasize the importance of proven therapies, such as blood pressure lowering, lipid lowering, and antiplatelet therapy, in patients with sleep apnea, who should be treated according to established guidelines for patients at elevated cardiovascular risk," they added.

This study was supported by the National Health and Medical Research Council of Australia. Dr. Yu reported having no relevant financial disclosures. His associates reported ties to numerous industry sources.

Continued from page 4

atopic asthma, and 38% were ex-smokers.

The researchers observed a significant reduction in the incidence of total asthma exacerbations in the azithromycin-treated group: 1.07/patient-year, compared with 1.86/patient-year in the placebo group, which translated into an incidence rate ratio of 0.59 (P less than .0001). Specifically, 127 patients in the placebo group (61%) experienced at least one asthma exacerbation, compared with 94 patients in the azithromycin group (44%; P less than .0001). A significant improvement in asthma-related quality of life was also seen among patients in the azithromycin group (adjusted mean difference of 0.36; $P = .001$).

Though the mechanism of the antiviral effect of macrolides is not yet determined, Dr. Gibson and his associates noted that respiratory viral infection is associated with severe exacerbations in eosinophilic asthma and causes most respiratory infections. "There is a known interaction between eosinophilic airway inflammation, exacerbation rate, and impaired innate antiviral immunity," they wrote. "Since we observed a

benefit of azithromycin on both asthma exacerbations and respiratory infections, we speculate that azithromycin might be acting to prevent viral-induced episodes in asthma."

"Given the major impact of asthma exacerbations on patients and the community and the ongoing risk posed by these events in patients who remain symptomatic on maintenance therapy, we consider that azithromycin is a valuable addition to existing regimens for treating asthma," the researchers concluded. "The long-term effects of this therapy on community microbial resistance require further evaluation."

The overall rates and types of serious adverse events seen in both groups were not significantly different from each other, with serious adverse events having occurred in 16 (8%) patients treated with azithromycin and 26 (13%) patients given the placebo.

The study was funded by the National Health and Medical Research Council of Australia and the John Hunter Hospital Charitable Trust. The authors reported having no financial conflicts directly related to the study.

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VIEW ON THE NEWS

Clinical – if not statistical – significance?

The estimated relative risk for the association between PAP and the composite outcome of acute coronary events, stroke, or vascular death was 0.77 in the study by Yu et al. It did not reach statistical significance but is similar to the estimated risk reduction associated with antiplatelet therapy, statins, and beta-blockers in preventing recurrent vascular events.

This magnitude of benefit could be of substantial clinical importance. Far from discouraging further research, this meta-analysis should be an impetus for more studies examining whether treatment of sleep apnea reduces vascular disease risk.

Daniel J. Gottlieb, MD, is in the medical service at the VA Boston Healthcare System and in the division of sleep medicine at Harvard Medical School, Boston. He reported receiving personal fees from VIVUS. Dr. Gottlieb made these remarks in an editorial accompanying Dr. Yu's report (JAMA. 2017;318:128-30).



RELEASE THE POTENTIAL OF NUCALA

The first subcutaneous anti-interleukin 5 (IL-5) targeted therapy for severe asthma with an eosinophilic phenotype

Indication

NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

ADVERSE REACTIONS

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

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

Benefits of NUCALA:

- **SIGNIFICANTLY REDUCED EXACERBATIONS* BY 53%** in the MENSA trial (NUCALA: 0.83/year vs placebo: 1.74/year; $P < 0.001$)¹
- **SIGNIFICANTLY REDUCED DAILY OCS DOSE WHILE MAINTAINING ASTHMA CONTROL**, in the SIRIUS trial (vs placebo; $P = 0.008$)²
- **IMPROVED QUALITY OF LIFE** in the MENSA trial (SGRQ responder rate: NUCALA, 71%, vs placebo, 55%; odds ratio: 2.1; 95% CI: 1.3, 3.2)[†]

Statistical hierarchy was not met; endpoint is exploratory and results are descriptive only.³

MENSA (Trial 2)¹: 32-week study comparing treatment with NUCALA or placebo, added to regular treatment with high-dose ICS and at least 1 other controller with or without OCS, in 576 patients with severe asthma with an eosinophilic phenotype.[‡]

Primary endpoint: Frequency of exacerbations.

SIRIUS (Trial 3)²: 24-week study comparing treatment with NUCALA or placebo in 135 patients with severe asthma with an eosinophilic phenotype[‡] who required at least 5 mg to 35 mg of prednisone equivalent per day in addition to regular use of high-dose ICS plus an additional controller.

Primary endpoint: Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control.

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

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

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

[‡]Identified by blood eosinophil counts ≥ 150 cells/ μ L at initiation of treatment (within 6 weeks of dosing) or ≥ 300 cells/ μ L in the past 12 months.

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothersbaby.org/asthma.

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

References: **1.** Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. **2.** Bel EH, Wenzel SE, Thompson PJ, et al; for the SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371(13):1189-1197. **3.** Data on file, GSK. **4.** Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J.* 2002;19(3):398-404.

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

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

BRIEF SUMMARY

NUCALA® (mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. [See *Clinical Studies (14) of full prescribing information.*]

Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued [see *Contraindications (4)*].

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo [see *Adverse Reactions (6.1)*]. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

- Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Opportunistic infections: herpes zoster [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

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

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation [see *Clinical Studies (14) of full prescribing information*]. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.2 Immunogenicity

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

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

6.3 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC [see *Data*].

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see *Use in Specific Populations (8.1)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mL at screening or greater than or equal to 300 cells/mL within 12 months prior to enrollment. [See *Clinical Studies (14) of full prescribing information.*] Subjects had a reduction in the rate of exacerbations

8.4 Pediatric Use (cont'd)

that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies [see *Adverse Reactions (6.1)*].

8.5 Geriatric Use

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

10 OVERDOSAGE

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

17. PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling*.

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

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

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothersbaby.org/asthma [see *Use in Specific Populations (8.1)*].

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NCL:2BRS

Tool predicts antimicrobial resistance in sepsis

BY HEIDI SPLETE

Frontline Medical News

Use of a clinical decision tree predicted antibiotic resistance in sepsis patients infected with gram-negative bacteria, based on data from 1,618 patients.

Increasing rates of bacterial resistance have “contributed to the unwarranted empiric administration of broad-spectrum antibiotics, further promoting resistance emergence across microbial species,” said M. Cristina Vazquez Guillamet, MD, of the University of New Mexico, Albuquerque, and her colleagues (Clin Infect Dis. cix612. 2017 Jul 10. doi: 10.1093/cid/cix612).

The researchers identified adults with sepsis or septic shock caused by bloodstream infections who were treated at a single center between 2008 and 2015. They developed clinical decision trees using the CHAID algorithm (Chi-squared Au-

tomatic Interaction Detection) to analyze risk factors for resistance associated with three antibiotics: piperacillin-tazobactam (PT), cefepime (CE), and meropenem (ME).

“[We] found good overall agreement between the accuracies of the [multivariable logistic regression] models and the decision tree analyses for predicting antibiotic resistance,” the researchers said.

Overall, resistance rates to PT, CE, and ME were 29%, 22%, and 9%, respectively, and 6.6% of the isolates were resistant to all three antibiotics.

Factors associated with increased resistance risk included residence in a nursing home, transfer from an outside hospital, and prior antibiotics

use. Resistance to ME was associated with infection with *Pseudomonas* or *Acinetobacter* spp, the researchers noted, and resistance to PT was associated with central nervous system and central venous catheter infections.

Clinical decision trees were able to separate patients at low risk for resistance to PT and CE, as well as those with a risk greater than 30% of resistance to PT, CE, or ME. “We also found good overall agreement between the accuracies of the [multivariable logistic regression] models and the decision tree analyses for predicting antibiotic resistance,” the researchers said.

The findings were limited by several factors, including the use of data from a single center and incomplete reporting of previous antibiotic exposure, the researchers noted. However, the results “provide a framework for how empiric antibiotics can be tailored according to decision tree patient clusters,” they said.

Ribaxamase prevented *C. difficile* infections by protecting microbiome

BY MICHELE G. SULLIVAN

Frontline Medical News

VIENNA – An investigational beta-lactamase reduced *Clostridium difficile* infections by 71% in patients receiving extended antibiotic therapy for respiratory infections but not by killing the opportunistic bacteria.

Rather, ribaxamase prevented *C. difficile* infections (CDI) by breaking down excess therapeutic antibiotics in the gut before they could injure an otherwise healthy microbiome, John Kokai-Kun, PhD, said at the European Society of Clinical Microbiology and Infectious Diseases annual congress.

“Up to 50% of an antibiotic dose is excreted into the small intestine, where it starts to disrupt the bowel microbiome and predisposes you to pick up *C. difficile*,” said Dr. Kokai-Kun, vice president of non-clinical affairs at Synthetic Biologics, Rockville, Md. “Ribaxamase is designed to block this cascade. If we protect the microbiome, any *C. difficile* that finds its way in would not find a gut conducive to the germination of vegetative cells.”

Ribaxamase is an oral enzyme that breaks the lactam ring in penicillins and cephalosporins. It’s formulated to release at a pH of 5.5 or higher, an environment that begins to develop in the upper small intestine near the bile duct – the same place that excess antibiotics are excreted.

“The drug is intended to be administered during, and for a short time after, intravenous administration of specific beta-lactam-containing antibiotics,” Dr. Kokai-Kun said. Ribaxamase doesn’t work on carbapenem-type antibiotics, he noted, and Synthetic Biologics is working on an effective

enzyme for those as well.

In early human studies, ribaxamase was well tolerated and didn’t interfere with the pharmacokinetics of therapeutic antibiotics (Antimicrob Agents Chemother. 2017 Mar;61[3]:e02197-16). It’s also effective in patients who are taking a proton pump inhibitor, he said.

Dr. Kokai-Kun reported the results of a phase 2b study of 412 patients who received IV ceftriaxone for lower respiratory infections. They were assigned 1:1 to either 150 mg ribaxamase daily or placebo throughout the IV treatment and for 3 days after.

The primary endpoint was prevention of *C. difficile* infection. The secondary endpoint was prevention of non-*C. difficile* antibiotic-associated diarrhea. An exploratory endpoint examined the drug’s ability to protect the microbiome. Patients were monitored for 6 weeks after treatment stopped.

The cohort was a mean 70 years old. One-third of patients also received a macrolide during their hospitalization, and one-third were taking proton pump inhibitors. The respiratory infection cure rate was about 99% in both groups at both 72 hours and 4 weeks.

Eight patients in the placebo group (3.8%) and two in the active group (less than 1%) developed *C. difficile* infection. That translated to a statistically significant 71% risk reduction, with a *P* value of



Michele G. Sullivan/Frontline Medical News

Dr. John Kokai-Kun

.027, Dr. Kokai-Kun said. Ribaxamase did not hit its secondary endpoint of preventing all-cause diarrhea or antibiotic-associated diarrhea that was not caused by *C. difficile* infection.

Although not a primary finding, ribaxamase also inhibited colonization by vancomycin-resistant enterococci, which occurred in about 70 (40%) patients in the placebo group and 40 (20%) in the ribaxamase group at both 72 hours and 4 weeks.

All patients contributed stool samples at baseline and after treatment for microbiome analysis. That portion of the study is still ongoing, Dr. Kokai-Kun said.

Synthetic Biologics sponsored the study and is developing ribaxamase. Dr. Kokai-Kun is the company’s vice president of nonclinical affairs.

msullivan@frontlinemedcom.com

On Twitter @alz_gal

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP,

comments: Aggressive treatment of septic patients with antibiotics has become the cornerstone of modern sepsis management.

Like all such treatments, adverse effects confound clinical outcomes.

Intensive care units have experienced epidemics of *C. difficile* colitis related to antibiotic use. The oral agent ribaxamase shows promise in this regard. This beta-lactamase breaks down surplus antibiotics in the gut and may offer needed adjunctive therapy to our sepsis regimens. Further study will be needed to confirm positive effects on clinical endpoints.



AR-301 holds promise for *S. aureus* pneumonia

BY DAMIAN MCNAMARA

Frontline Medical News

NEW ORLEANS – Monoclonal antibody therapies have already upended treatment strategies in cancer, dermatology, and multiple inflammatory diseases, and infectious disease may be next.

That's because a single injection of a monoclonal antibody in development, AR-301, appeared to be safe and effective as an adjunct treat-

poster presentation at the annual meeting of the American Society for Microbiology.

Treatment started within 36 hours of onset of severe pneumonia. Severity was based on a mean

PaO₂/FiO₂ of 147 and/or a need for catecholamine. Six cases of pneumonia were related to MRSA and the remaining 42 to methicillin-susceptible *S. aureus*. The mean APACHE II score was 18.7, the

mean Clinical Pulmonary Infection Score was 9.6, and the mean Sequential Organ Failure Assessment score was 6.9.

Participants were recruited from

Continued on following page



Dr. Celine Gonzalez

ment for severe pneumonia caused by *Staphylococcus aureus*, according to a new study. The monoclonal antibody attacks the alpha-toxin secreted by *S. aureus*, thereby helping to protect immune cells.

Researchers assessed 48 patients between May 2012 and May 2016 in a randomized, double-blind, placebo-controlled trial. Each participant received a single injection of placebo or AR-301 (at one of four doses) to test the antibody's tolerability and effectiveness.

"We know *S. aureus* pneumonia is a big problem. There is a lot of antibiotic resistance, and that is why we need new treatments," Celine Gonzalez, MD, of the Dupuytren Central University Hospital in Limoges, France, said in an interview.

"Animal studies have shown the monoclonal antibody seems to be useful. This is the first in-human study to use a monoclonal antibody to treat hospital-acquired pneumonia due to *Staphylococcus aureus*," Dr. Gonzalez said in a late-breaking

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

SLOW THE PATH OF IPF PROGRESSION

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

DISCOVER MORE ABOUT OFEV INSIDE.

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS
Hepatic Impairment

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

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



OFEV[®]
 (nintedanib)
 capsules 150mg

TREAT NOW. SLOW PROGRESSION.

Continued from previous page

13 ICUs in four countries. About 80% of participants were men. Their mean age was 56 years, and mean body mass index was 29 kg/m². Concurrent antibiotic treatment choice and duration were at the investigator's discretion.

S. aureus infection was considered eradicated if a follow-up culture was

“Animal studies have shown the monoclonal antibody seems to be useful. This is the first in-human study to use a monoclonal antibody to treat hospital-acquired pneumonia due to Staphylococcus aureus,” Dr. Celine Gonzalez said.

negative, a result achieved by 63% of the 16 placebo patients and 75%-88% of the AR-301-dosage groups.

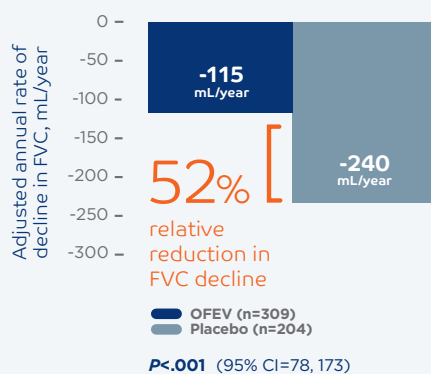
Eradication was also based on observed clinical success in the absence of a confirmatory culture. This was

achieved by 38% in the placebo group and 13%-25% of the monoclonal antibody cohorts. A total of seven placebo patients and 15 AR-301 patients met eradication by these criteria.

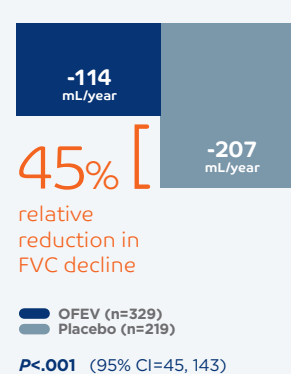
Side effects were primarily minor and transient, Dr. Gonzalez said. Of the 343 total adverse events reported, only 8 (2.3%) were considered treatment related, she added.

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

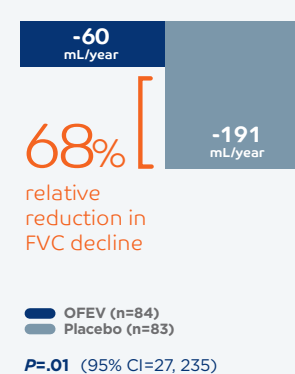
INPULSIS[®]-1 (Study 2)^{3,4}



INPULSIS[®]-2 (Study 3)^{3,4}



TOMORROW (Study 1)^{3,5}



CI, confidence interval.

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes

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

Gastrointestinal Disorders

Diarrhea

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

Nausea and Vomiting

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

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



ONE CAPSULE, TWICE DAILY WITH FOOD³

Not shown at actual size

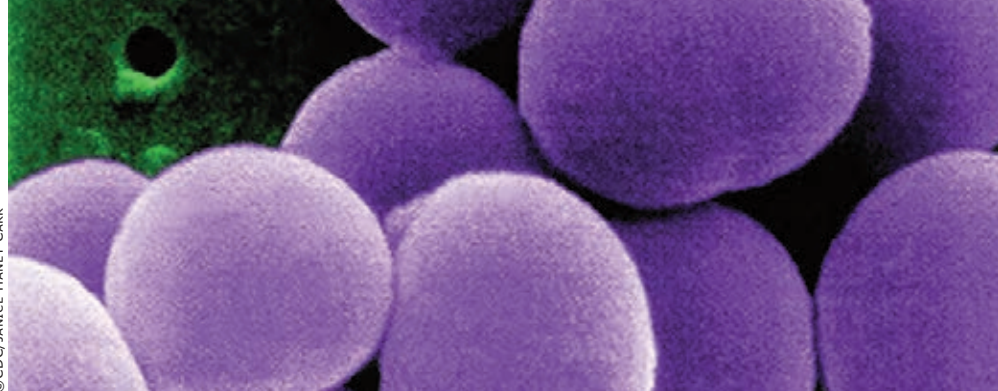
“In infectious disease, it’s the beginning” for monoclonal antibody therapy, Dr. Gonzalez said. “But, it appears to be the future because ... it is a more specific treatment, and there is no resistance.”

The study suggests adjunctive treatment with AR-301 appears safe for treatment of hospital-acquired bacterial pneumonia, she noted.

The next step will be to confirm the findings in a larger, follow-up study that includes more efficacy outcomes, Dr. Gonzalez added.

Dr. Gonzalez reported having no relevant disclosures. The study’s principle investigator is a scientific advisor for Aridis Pharmaceuticals, which is developing AR-301.

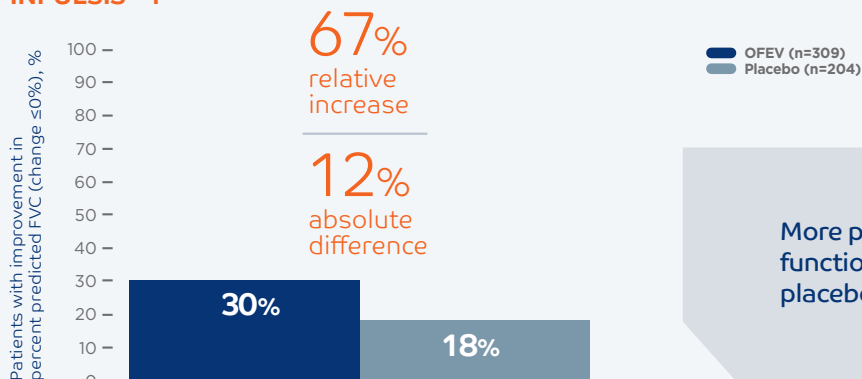
chestphysician@frontlinemedcom.com



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

INPULSIS®-1³

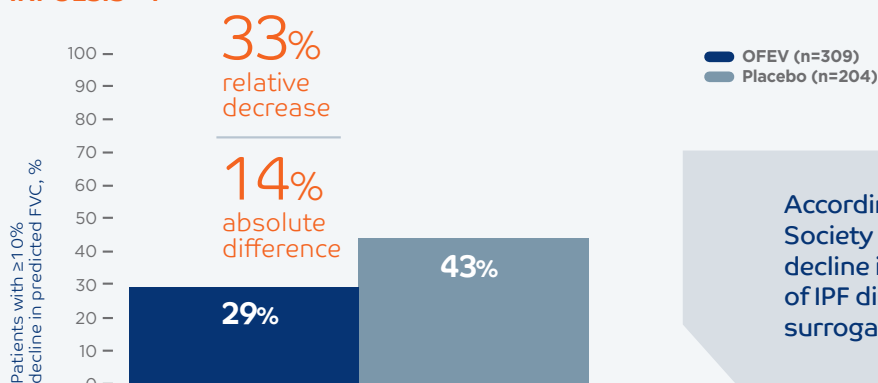


More patients had improved lung function with OFEV than with placebo in the INPULSIS® trials³

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

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

INPULSIS®-1^{3,6-8}



According to American Thoracic Society (ATS) guidelines, ≥10% FVC decline is an established measure of IPF disease progression and a surrogate marker in mortality^{6,7,9}

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

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

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT’D)

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

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



RV contractility improved in scleroderma-PAH

BY M. ALEXANDER OTTO
Frontline Medical News

A combination of ambrisentan (Letairis) and tadalafil (Cialis) improves regional and global

right ventricular contractility in patients with scleroderma-associated pulmonary arterial hypertension, according to an open-label investigation of 23 patients.

The project was a follow-up to

a previous report showing that the upfront combination – tadalafil 40 mg and ambrisentan 10 mg oral once daily – improved hemodynamics, right ventricular (RV) structure and function, and

functional status in treatment-naive patients after 36 weeks and “may represent a very effective therapy for this patient population” (Am J Respir Crit Care Med. 2015 Nov 1;192[9]:1102-10).

OFEV is only available through participating specialty pharmacies

TO GET YOUR APPROPRIATE PATIENTS WITH IPF STARTED ON OFEV:



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



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



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

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

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

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

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

OFPROFISIFEB16

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



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TREAT NOW. SLOW PROGRESSION.



DR. MERCURIO

Survival in scleroderma pulmonary arterial hypertension (PAH) depends mostly on RV function, so investigators in the follow-up study wanted to take a closer look at how the combination affected the heart. They reviewed conventional echocardiograph imaging and RV strain

analyses for the 23 of the 24 patients in the original trial for which it was available (Am J Respir Crit Care Med. 2017 Jun 29. doi: 10.1164/rccm.201704-0789LE).

At baseline, the subjects had normal left ventricular (LV) size and function, with borderline left atrial enlargement

and mild LV diastolic dysfunction. Their right heart chambers were significantly dilated, with RV hypertrophy. Conventional RV function parameters – tricuspid annular systolic plane excursion (TAPSE) and fractional area change (FAC) – were impaired. RV systolic pressure (RVSP) was severe-

ly elevated. There was also a marked reduction of global RV longitudinal systolic strain (RVLSS), compared with normal values, mainly because of a reduction in midventricular and apical RVLSS, with relative hyperkinesis of basal RVLSS.

Continued on following page

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

CONTRAINDICATIONS: None

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

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

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

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

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

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain ^a	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation ^b	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous 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

Amplatzer devices outperform oral anticoagulation

BY BRUCE JANCIN

Frontline Medical News

PARIS – Percutaneous left atrial appendage closure with an Amplatzer device in patients with nonvalvular

atrial fibrillation was associated with significantly lower rates of all-cause and cardiovascular mortality, compared with oral anticoagulation, in a large propensity score–matched observational registry study.

Left atrial appendage closure (LAAC) also bested oral anticoagulation (OAC) with warfarin or a novel oral anticoagulant (NOAC) in terms of net clinical benefit on the basis of the device therapy’s greater protection

against stroke and systemic embolism coupled with a trend, albeit not statistically significant, for fewer bleeding events, Steffen Gloekler, MD, reported at the annual congress of the European Association of Percutaneous

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

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

may reduce fertility in females of reproductive potential [see Use in Specific Populations]. Counsel patients on pregnancy prevention and planning. **Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV [see Dosage and Administration, Warnings and Precautions and Use in Specific Populations]. **Contraception:** Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. **Infertility:** Based on animal data, OFEV may reduce fertility in females of reproductive potential. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily [see Dosage and Administration]. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients [see Dosage and Administration]. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see Warnings and Precautions]. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV. **OVERDOSAGE:** In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

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

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Rx only



Continued from previous page

After 36 weeks of treatment, right heart chamber sizes were significantly reduced. There was also a decrease in RV free wall thickness, which coincided with a significant reduction in RV mass on cardiac MRI. TAPSE, FAC, and global RVLSS improved significantly, and RVSP decreased significantly. LV end-diastolic and end-systolic diameters and volumes increased significantly.

The changes “may represent transition from maladaptive RV remodeling ... to a more physiological and adaptive RV remodeling;” however, “the effects of treatment should be interpreted with caution, as this was an open-label study without a placebo or a single-drug control group,” said investigators led by Valentina Mercurio, MD, a postdoc fellow at Johns Hopkins University, Baltimore.

Subjects were about 60 years old on average, and most were women. The majority shifted from World Health Organization PAH functional class 3 to 2 during the original trial. Mean 6-minute walk tests increased from 341 m to 401 m.

Gilead and United Therapeutics provided the ambrisentan and tadalafil. Dr. Mercurio reported funding from both companies and Merck. The original study was sponsored by United Therapeutics.

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VIEW ON THE NEWS

Jason Lazar, MD, FCCP, comments: Dual therapy is standard therapy for PAH but not for secondary pulmonary hypertension. Dual oral therapy represents a novel approach for treatment, and very few studies have demonstrated any drug to benefit secondary pulmonary hypertension.



Cardiovascular Interventions.

The Watchman LAAC device, commercially available both in Europe and the United States, has previously been shown to be superior to OAC in terms of efficacy and noninferior regarding safety. But there have been no randomized trials of an Amplatzer device versus OAC. This lack of data was the impetus for Dr. Gloekler and his coinvestigators to create a meticulously propensity-matched observational registry.

Five hundred consecutive patients with AF who received an Amplatzer Cardiac Plug or its second-generation version, the Amplatzer Amulet, during 2009-2014 were tightly matched to an equal number of AF patients on OAC based on age, sex, body mass index, left ventricular ejection fraction, renal function, coronary artery disease status, hemoglobin level, CHA₂DS₂-VASc score, and HAS-BLED score. During a mean 2.7 years, or 2,645 patient-years, of follow-up, the composite primary efficacy endpoint, composed of stroke, systemic embolism, and cardiovascular or unexplained death occurred in 5.6% of the LAAC group, compared with 7.8% of controls in the OAC arm, for a statistically significant 30% relative risk reduction. Disabling stroke occurred in 0.7% of Amplatzer patients versus 1.5% of controls. The ischemic stroke rate was 1.5% in the device therapy group and 2% in the OAC arm.

All-cause mortality occurred in 8.3% of Amplatzer patients and 11.6% of the OAC group, for a 28% relative risk reduction. The cardiovascular death rate was 4% in the Amplatzer group, compared with 6.5% of controls, for a 36% risk reduction.

The composite safety endpoint, comprising all major procedural adverse events and major or life-threatening bleeding during follow-up, occurred in 3.6% of the Amplatzer group and 4.6% of the OAC group, for a 20% relative risk reduction that is not significant at this point because of the low number of events. Major, life-threatening, or fatal bleeding occurred in 2% of Amplatzer recipients versus 5.5% of controls, added Dr. Gloekler of University Hospital in Bern, Switzerland.

The net clinical benefit, a composite of death, bleeding, or stroke, occurred in 8.1% of the Amplatzer group, compared with 10.9% of controls, for a significant 24% reduction in relative risk in favor of device therapy.

Of note, at 2.7 years of follow-up only 55% of the OAC group were still taking an anticoagulant: 38% of the original 500 patients were on warfarin, and 17% were taking a NOAC. At that point, 8% of the

Amplatzer group were on any anti-coagulation therapy.


Discussion of the study focused on that low rate of medication adherence in the OAC arm. Dr. Gloekler's response was that, after looking at the literature, he was no longer surprised by the finding that only 55% of the control group were on OAC at follow-up.

"If you look in the literature, that's exactly the real-world adherence for OACs. Even in all four certification trials for the NOACs, the rate of discontinuation was 30% after 2 years – and these were controlled studies. Ours was observational, and it depicts a good deal of the problem with any OAC in my eyes," Dr. Gloekler said.

Patients on warfarin in the real-world Amplatzer registry study spent on average a mere 30% of time in the therapeutic international normalized ratio range of 2-3.

Dr. Gloekler reported receiving research funds for the registry from the Swiss Heart Foundation and Abbott.

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
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References: 1. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis.* 2008;3(3):371-384. 2. Braido F, Lavorini F, Blasi F, Baiardini I, Canonica GW. Switching treatments in COPD: implications for costs and treatment adherence. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2601-8.

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Biomarker distinguishes ARDS, acute heart failure

BY MITCHEL L. ZOLER

Frontline Medical News

WASHINGTON – Plasma levels of an interleukin-33 receptor that's involved in inflammation regulation appeared able to discriminate between acute respiratory distress syndrome and acute decompensated heart failure in an analysis with 72 patients.

In a second study, high plasma levels of the same interleukin-33 receptor, soluble suppressor of tumorigenicity 2 (sST2), identified acute respiratory distress syndrome (ARDS) patients who were sicker and more responsive to conservative fluid management, Sean D. Levy, MD, said at an international conference of the American Thoracic Society.

While further validation of sST2 is needed, its future as a clinically useful biomarker also depends on development of a test that could be easily and repeatedly used at the bedside, said Dr. Levy, a pulmonologist at New England Deaconess Medical Center in Boston. "We're not quite there yet," he explained. The sST2 test he used for his studies is sold by Critical Diagnostics.

In order to assess the ability of sST2 to reliably distinguish patients with ARDS from those with acute decompensated heart failure, he and his associates selected 72 patients seen at the Massachusetts General Hospital in Boston with an initial diagnosis of acute decompensated heart failure accompanied by bilateral lung infiltrates and acute hypoxemia respiratory failure requiring endotracheal intubation and mechanical ventilation. The investigators measured the sST2 level in a plasma specimen from each patient. In addition, after each patient either left the hospital or died, their case underwent

review by two critical care physicians who retrospectively rediagnosed the patients as either having ARDS or acute decompensated heart failure. This divided the cohort into 30 patients with ARDS and 42 with true acute heart failure. The two subgroups matched up fairly closely for most clinical measures and comorbidities, but APACHE III (Acute Physiology and Chronic Health Evaluation III) scores averaged significantly higher in the ARDS patients.

The plasma levels of sST2 showed a dramatic split between the two subgroups. The 30 patients retrospectively diagnosed with ARDS had an average level of 386 ng/mL with an interquartile range of 318-611 ng/mL. The 42 acute decompensated heart failure patients averaged a sST2 level of 148 ng/mL, with an interquartile range of 84-225 ng/mL. The area under the receiver operator curve for discriminating between ARDS and acute heart failure using a cutpoint of 271 mg/mL was 0.86, showing "good" discrimination, Dr. Levy said. This cutpoint had a sensitivity of 83% and specificity of 88% for correctly distinguishing between ARDS and acute heart failure.

In a second analysis, Dr. Levy and his associates looked at the ability of sST2 levels to separate out patients with acute lung injury who had a more robust response to either the conservative or liberal fluid-management strategies tested in the Fluid and Catheter Treatment Trial (FACTT), run by the National Heart, Lung, and Blood Institute's ARDS Clinical Trials Network. The primary outcome of

FACTT was death from any cause 60 days after entry, and this showed no significant difference between conservative (restricted fluids and increased urine output) and liberal (the reverse) fluid management strategies in acute lung injury patients (N Engl J Med. 2006 Jun 15;354[14]:2564-75). From among

the 1,001 patients enrolled in FACTT, 826 had specimens available for measuring sST2 (Crit Care Med. 2013 Nov;41[11]:2521-31). The researchers applied the sST2 cut point they derived in the first analysis to the FACTT cohort and identified 133 (16%) patients with a low sST2 level and 693 (84%) with a high

The plasma levels of sST2 showed a dramatic split between the two subgroups.



DR. LEVY

level. The patients with high sST2 had significantly higher APACHE III scores, worse acidemia, and worse renal function.

Patients with high sST2 levels had a significant increase in ventilator-free days on conservative fluid management, compared with liberal management, while the two management strategies produced virtually identical results in the patients with low levels of sST2. Patients with high sST2 also had a significantly quicker time to extubation on a conservative strategy, compared with the liberal strategy, and again this correlation did not exist among patients with low sST2. However, as in the overall trial, a conservative strategy had no discernible impact on 60-day mortality, compared with the liberal strategy, even in the subgroup with high sST2.

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More pulmonary patients getting palliative care

BY RICHARD FRANKI

Frontline Medical News

Patients referred to palliative care are most likely to have cancer, but the proportion has gone down since 2009 as other diagnoses have

increased, according to a report from the National Palliative Care Registry.

In 2015, cancer patients made up 26% of the patients referred to palliative care, compared with 35% in 2009. The situation was reversed for the next three most common diagno-

ses in 2015: Cardiac diagnoses rose from 5% in 2009 to 13%, pulmonary diagnoses increased from 6% to 12%, and neurologic diagnoses went from 3% to 8%, the report showed.

Referrals by specialty were led by hospital medicine, which accounted for 48% of all patients referred to palliative care in 2015, with internal medicine/family medicine next at 14%, followed by pulmonary/critical care at 13% and oncology at 7%.

An increase in overall palliative care penetration was seen from 2009 to 2015, as the percentage of annual hospital admissions seen by a palliative care team increased from 2.7% to 4.8%. Over that same period, the percentage of palliative care patients who died in the hospital decreased from 29% to 22%, according to the report.

In 2015, there were 420 palliative care programs participating in the registry, which is a joint project of the Center to Advance Palliative Care and the National Palliative Care Research Center.

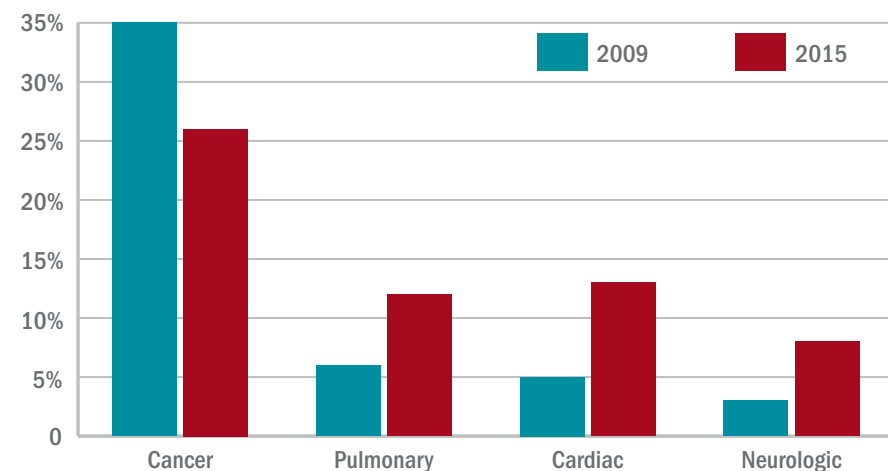
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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: "But doc, isn't hospice just for cancer patients?"

My 80-year-old patient has COPD, requires oxygen at 4 L/min at rest, and cannot walk to his mailbox despite being on a maximum bronchodilator regimen. Too old to be a candidate for lung transplant, I have few additional medical treatments to offer him. I hope that I can help him have comfort during the last days of his life. My response to him is: "Not any longer." The study from the National Palliative Care Registry demonstrates that pulmonary physicians and their patients are increasingly aware that palliation plays an important role in the management of patients with end-stage respiratory disease.

Leading diagnosis groups referred to palliative care



FRONTLINE MEDICAL NEWS

Note: Based on data from the National Palliative Care Registry.

Source: Center to Advance Palliative Care, National Palliative Care Research Center

Patients report issues with home O₂

BY KATIE WAGNER LENNON

Frontline Medical News

WASHINGTON – Patient education in the use of home oxygen halves the number of system use issues reported by patients, based on results of a survey of nearly 2,000 patients.

Pulmonary clinicians and patients report “intolerable barriers to home oxygen services,” lead researcher Susan S. Jacobs, RN, MS, said in a poster session at an international conference of the American Thoracic Society. These barriers include insufficient oxygen supply, inadequate and physically unmanageable portable options, and equipment malfunction.

In their study, Ms. Jacobs and her colleagues sought to determine the frequency and types of problems experienced by adult home oxygen users in the United States. Survey

Patients who were educated by a health-care professional reported fewer problems and were more likely to report having no problems with their oxygen system. Of the patients who received oxygen therapy instruction from a health-care professional, 76 (57%) did not report having any issues with their system. In contrast, of the patients who received no instruction, 116 (64%) said they had problems with their oxygen.

Most survey participants (1,113 patients) received oxygen therapy instruction from an oxygen delivery person instead of a health-care professional. This group’s opinions about their oxygen systems were split, with 51% (563 patients) experiencing issues with their systems. The other 49% reported no problems.

Survey participants most frequently complained that their

“We’ve demonstrated that, if the patients are educated by a health-care professional, the problems with oxygen go down, said Susan Jacobs, who is a nurse coordinator in the division of pulmonary and critical care medicine at Stanford University.”

respondents were recruited via efforts by the ATS Public Advisory Roundtable. Links to the survey were posted on various patient advocacy websites, and flyers were posted at clinics and pulmonary rehabilitation programs asking patients to participate in an online, 60-item survey developed by the ATS Nursing Oxygen Working Group. Participants included 1,926 patients, but not all patients responded to every question.

“We’ve demonstrated that, if the patients are educated by a health-care professional, the problems with oxygen go down, Ms. Jacobs, who is a nurse coordinator in the division of pulmonary and critical care medicine at Stanford (Calif.) University, said in an interview. “While physicians can provide oxygen for their patients, the patient oxygen education will most likely lie with the nurses and respiratory therapists.”

Of patients who responded to the survey question “Do you have oxygen problems?” 51% (899) said yes. On average, these patients said they had experienced 3.5 types of problems with their systems.

equipment was not working; 499 selected this response to the question, “What types of oxygen problems do you have?”

Many patients also reported being unable to spend as much time out of their homes as they wanted. This limitation resulted from their lack of access to functioning, manageable, high-flow, portable oxygen systems, according to the researchers. Further, 43% of patients reported that their portable system limited their activity outside the home frequently or all of the time.

“Most of the reported problems were related to respondents not having portable systems that let them be out of their house for more than 2-4 hours or [to systems that] were too heavy for the patients to lift up and down their stairs and out of their cars, and they had problems operating them,” Ms. Jacobs said.

The survey respondents also reported experiencing delivery problems, not being able to change the company providing them with oxygen, receiving incorrect or delayed orders from a physician, or being unable to get liquid oxygen. These



COURTESY SUSAN JACOBS

Susan S. Jacobs instructs a patient on how to use home oxygen.

responses were provided by 267, 177, 166, and 68 patients, respectively.

“There is a lot of confusion for the physicians as well as the nurses about what types of systems the patients can use [and] the pros and cons of each system. There’s lots of confusion and time spent about getting the initial orders right, getting them set up with a supplier, and ensuring the patient gets the equipment that was ordered. There is a lot of back and forth, which results in a delay to the patient, and the patients are upset because they are waiting for their oxygen supply,” she explained. “So, I think that physicians are very much wanting clarification to streamline the process and identify what patient systems are appropriate, which are high flow, [and] what their patients’ needs are to help physicians spend less time on this and help the patients get their oxygen set up in a timely manner.”

The study participants came from all 50 states and were 64 years of age on average and mostly women. A high percentage (39%) of the sample

had chronic obstructive pulmonary disease, while 26% had interstitial lung diseases, 18% had pulmonary arterial hypertension, 8% had alpha-1 antitrypsin deficiency, and 4% had lymphangioleiomyomatosis.

Ms. Jacobs noted that she thought patients would benefit from greater physician knowledge of their prescribing options.

“A physician can dictate exactly what system they want. ... You can try to give [patients] a lighter system, a backpack, a smaller tank, more tanks per week, depending on their lifestyle and their needs. But physicians, a lot of times, like all of us and our patients, [are] not aware of all these choices,” she said during the interview.

An online resource providing all of the pros and cons of the different types of portable oxygen systems that would be appropriate for physicians, nurses, and patients, as well as an examination of the quality standards of the oxygen suppliers, are needed, she noted.

Ms. Jacobs reported no financial disclosures.

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VIEW ON THE NEWS

Vera A. De Palo, MD, MBA, FCCP, comments: The authors point out that there are a multitude of reasons that a patient may have difficulty with oxygen therapy. Their work would seem to indicate that conversation between the care team members (patient/family, physician, and respiratory therapy provider) can help reduce the questions and difficulties that a patient and his/her family may have after the prescribed therapy has been delivered. Any action that would enhance the likelihood of compliance with the prescribed therapy would be a benefit to our patients.





Take a different path

*INDICATIONS

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

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

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

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

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

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

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


CONTRAINDICATIONS

Adempas is contraindicated in:

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

WARNINGS AND PRECAUTIONS

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



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

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

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

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

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

WARNINGS AND PRECAUTIONS (continued)

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

Important requirements of the Adempas REMS Program include the following:

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

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

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

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

WARNINGS AND PRECAUTIONS (continued)

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

MOST COMMON ADVERSE REACTIONS

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

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



Bayer
100 Bayer Boulevard, Whippany, NJ 07981 USA
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PP-400-US-3547 May 2017

ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION

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

WARNING: EMBRYO-FETAL TOXICITY

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

1 INDICATIONS AND USAGE

1.1 Chronic-Thromboembolic Pulmonary Hypertension

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

1.2 Pulmonary Arterial Hypertension

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

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

4 CONTRAINDICATIONS

4.1 Pregnancy

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

4.2 Nitrates and Nitric Oxide Donors

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

4.3 Phosphodiesterase Inhibitors

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

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

5.2 Adempas REMS Program

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

Important requirements of the Adempas REMS Program include the following:

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

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

5.3 Hypotension

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

5.4 Bleeding

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

5.5 Pulmonary Veno-Occlusive Disease

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

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

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

7.2 Pharmacokinetic Interactions with Adempas

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Females and Males of Reproductive Potential

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

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

8.7 Renal Impairment

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

8.8 Hepatic Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

Embryo-Fetal Toxicity

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

Adempas REMS Program

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

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

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

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

Other Risks Associated with Adempas

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

Manufactured for:



Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

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6710504BS

Algorithm for identifying IPF has low PPV

BY M. ALEXANDER OTTO

Frontline Medical News

ICD-9 codes were poor at picking out idiopathic pulmonary fibrosis patients from administrative databases for epidemiologic studies, but a new tool could improve diagnostic accuracy, according to Kaiser Permanente and University of California, San Francisco, investigators.

“In the age of large administrative databases and electronic medical records, there is rich opportunity to conduct population-based studies” of disease behavior, outcomes, health care use, and other matters, but researchers first need to be able to accurately identify patients with idiopathic pulmonary fibrosis (IPF) in large data sets, said investigators led by Brett Ley, MD, an assistant professor of medicine at UCSE.

The research community has

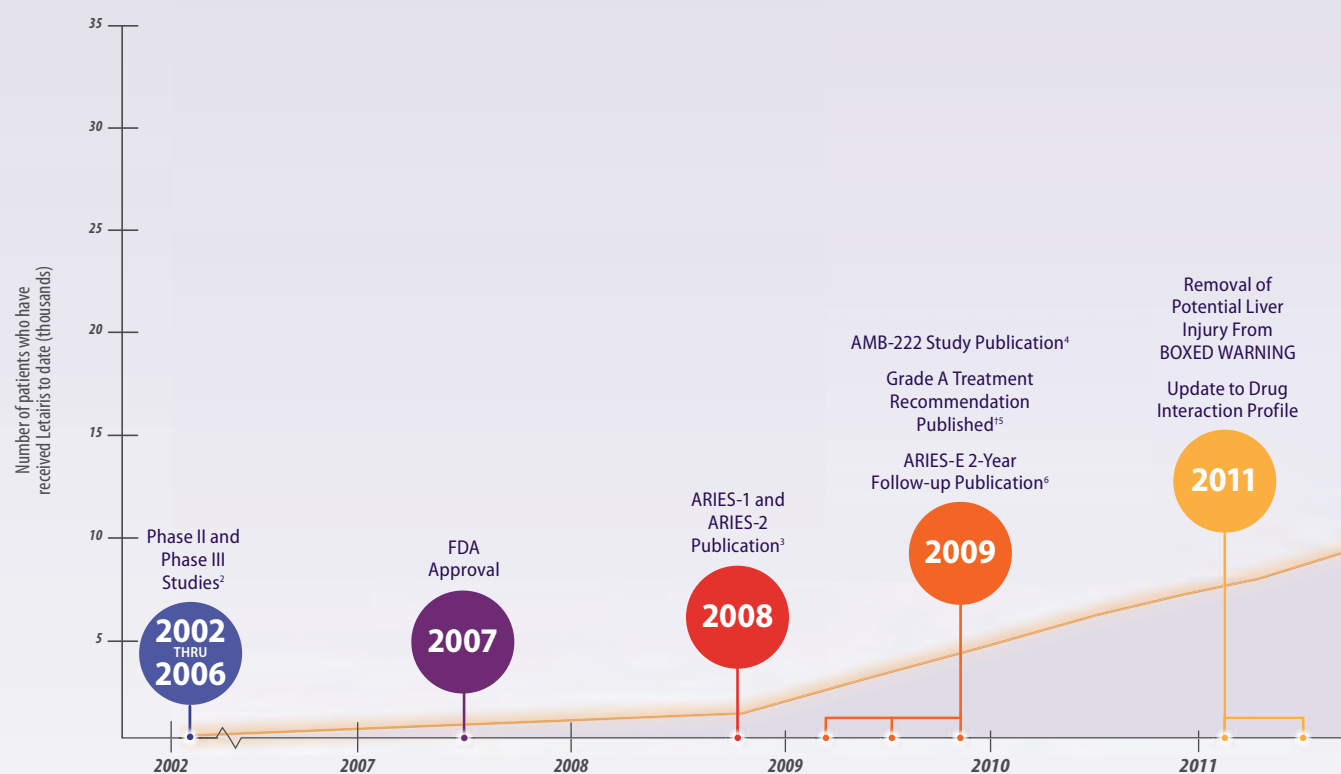
traditionally relied on claims for specific IPF diagnostic codes – ICD-9 code **516.3** or ICD-9-CM code **516.31** – to identify patients, but the approach had never been validated. To see how well it works,

the investigators applied it to the nearly 5.4 million adults in the Kaiser Permanente Northern California system during 2000-2014. After patients with interstitial lung disease-associated codes entered

on or after the day of the last IPF code were excluded, the algorithm identified 2,608 patients as having IPF (*Ann Am Thorac Soc.* 2017 Jun;14[6]:880-7).

Next, the investigators randomly

Confidence built from over a decade of clinical experience



*More than 35,000 patients have been prescribed Letairis since July 9, 2007. Based on LEAP database March 2017.⁷

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

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

[§]Based on 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Class I Recommendation: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; is recommended/is indicated. Level of Evidence: B: Data derived from a single randomized clinical trial or large non-randomized studies.⁵

Indication

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

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

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

Important Safety Information

BOXED WARNING: EMBRYO-FETAL TOXICITY

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

VIEW ON THE NEWS

Case validation is key

This study glaringly displays potential problems with using ICD codes for research purposes and calls into question results from a handful of studies that yielded epidemiological estimates for idiopathic pulmonary fibrosis. We are reminded that practitioner-generated diagnostic codes of IPF recorded in the medical record are subject to inaccuracies, which can be illuminated by the “gold standard” – multidisciplinary adjudication.

Moving forward, particularly as longitudinal, nationwide IPF registries come online, patient-level case validation should be employed. As we move into the era of ICD-10, the study should serve as a call to improve IPF case ascertainment accuracy for any investigators choosing to use large data analytic strategies. Doing so will mute the background noise and allow us to better hear the signals of this complex disease.

Evans R. Fernandez Perez, MD, is a pulmonologist at National Jewish Health, Denver. He made his comments in an editorial, and reported speaker's fees from Boehringer Ingelheim and Genentech (Ann Am Thorac Soc. 2017 Jun;14[6]:829-30).

selected 150 of those patients and examined their medical records, procedure codes, CTs, and other patient-level data to see how many of them really had IPF. The results weren't good. The positive predictive value of the IPF code-based algorithm was only 42.2%, with a sensitivity of 55.6%.

The widely used code-based IPF

algorithm does “not generate accurate estimates of IPF incidence and prevalence. ... Over half of the patients identified as having IPF ... did not have IPF on case review. Alarming, whereas half of the misclassified cases had an alternative [interstitial lung disease] diagnosis, the other half had no clinical or radiologic evidence of ILD [interstitial

lung disease] at all.” The algorithm also “likely misses a substantial proportion of patients who do have IPF,” Dr. Ley and his colleagues said.

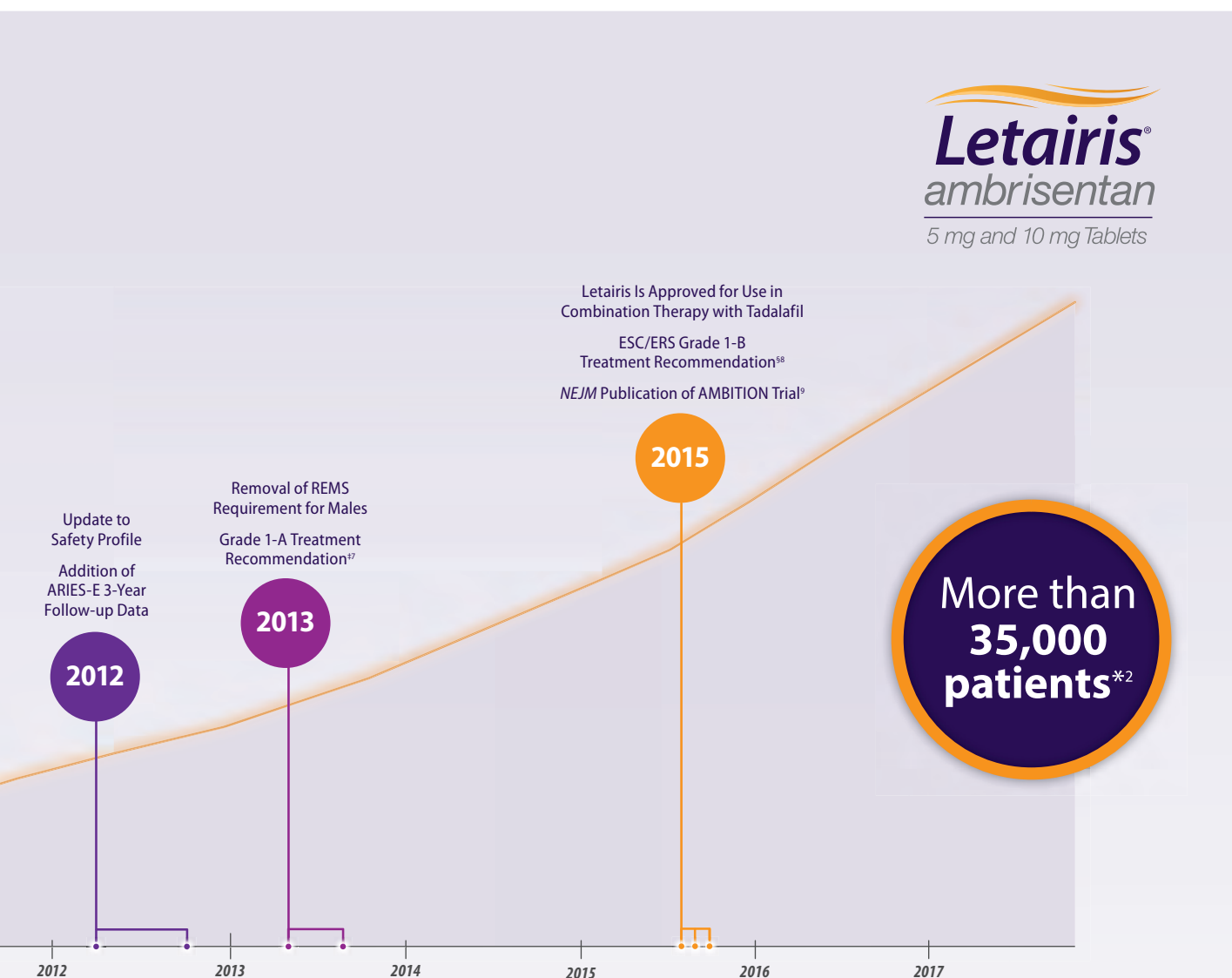
“We can only speculate about the reasons. ... It seems likely to be due to a combination of misdiagnosis at the clinical level and miscoding at the administrative level,” they said.

To try to improve the situation,

the team tweaked the algorithm to include only patients 50 years or older who had at least two 516.3 or 516.31 claims 1 month or more apart and a chest CT procedure code beforehand. They again excluded ILD-associated claims on or after the day of the last IPF code.

Although the sensitivity of the

Continued on following page



Important Safety Information (continued)

Contraindications

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

Warnings and Precautions

- **Embryo-fetal toxicity and Letairis REMS Program requirements:**
 - Prescribers must be certified with the program by enrolling in and completing training
 - All female patients, regardless of reproductive potential, must enroll in the Letairis REMS Program
 - Male patients are not enrolled in the program
 - Pharmacies must be certified with the program and must dispense to female patients who are authorized to receive Letairis
- Further information is available at www.letairisrems.com or 1-866-664-5327.
- **Peripheral edema:** Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. Further evaluate patients who develop clinically significant fluid retention to determine the cause and possible need for edema treatment or to discontinue Letairis. In clinical studies, peripheral edema was more common with Letairis than with placebo (most edema was mild to moderate in severity); and with Letairis plus tadalafil than with either drug alone. There have also been postmarketing reports of fluid retention occurring within weeks after starting Letairis that required a diuretic, fluid management, or hospitalization for decompensating heart failure
- **Pulmonary edema with pulmonary veno-occlusive disease (PVOD):** Consider PVOD in patients who develop acute pulmonary edema during Letairis initiation and discontinue Letairis if PVOD is confirmed
- **Decreased sperm counts** have been observed in patients taking endothelin receptor antagonists and in animal fertility studies with ambrisentan. Counsel patients about potential effects on fertility

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

modified algorithm was lower than the original, it had a more robust positive predictive value of 70.4% in the derivation cohort and 61.8% in the validation cohort, both derived from the 150 patients used to validate the original algorithm.

“By making a few simple, empirically derived changes to the IPF

algorithm,” it’s possible to “more reliably [identify] patients” with IPF. “We believe the modified IPF algorithm will be useful for population-based studies of IPF ... that require high diagnostic certainty,” the investigators concluded.

The traditional algorithm found an incidence of 6.8 cases per 100,000 person-years, which was on the low

end of previous reports, perhaps because of the relative health and youth of the 5.4 million patient pool. As in past studies, IPF incidence increased with older age and was highest in white patients and men.

The researchers called for further study of whether the more specific codes will allow for improved case classification of IPF.

The work was funded by the National Institutes of Health. Dr. Ley reported speaker’s fees from Genentech, and another author was an employee of Genentech. The senior author Harold Collard, MD, an associate professor in UCSF’s division of pulmonary and critical care medicine, reported personal fees from various companies.

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

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

Adverse Reactions

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

Drug Interactions

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

Use in Specific Populations

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

Dosage and Administration

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

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

Letairis
ambrisentan
5 mg and 10 mg Tablets

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

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

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals [see *Contraindications, Warnings and Precautions, Use in Specific Populations*].

Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and one month after discontinuation of treatment [see *Dosage and Administration, Use in Special Populations*].

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program [see *Warnings and Precautions*].

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

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

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

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

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

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

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

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

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

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

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

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

GI disorder risk may rise in poorly controlled asthma

BY BRIAN HOYLE

Frontline Medical News

SAN FRANCISCO – Pediatric patients who have asthma that is poorly controlled may be more likely to

have functional gastrointestinal (GI) disorders, which feature chronic GI distress that has several causes, according to a study of patients treated at one hospital.

Female sex and increased anxiety

were influential factors.

“This study suggests a high prevalence of functional GI disorders among patients with persistent asthma. Moreover, patients with functional GI disorders had poor asthma

control and increased anxiety. Clinicians should consider functional GI disorders in patients with poor asthma control and assess for anxiety as indicated,” Ruben J. Colman, MD, a pediatric resident at SBH Health System, New York, said at the Pediatric Academic Societies meeting.

The prospective, cross-sectional study recruited patients aged 4-20 years at the emergency department, pediatric inpatient unit, and ambulatory clinics at St. Barnabas Hospital, a 422-bed, not-for-profit, acute care community hospital. Those with persistent asthma, which was evident by an ongoing history of daily inhaled corticosteroid medication, were enrolled.

Functional GI disorders including functional abdominal pain, irritable bowel syndrome, and functional dyspepsia were evaluated. The study was prompted by the knowledge that these conditions are a common cause of chronic GI symptoms in children, and from the findings of a retrospective study of 30,000 patients in Europe that reported a higher prevalence of asthma in those with functional GI disorders, compared with those without chronic GI distress (Aliment Pharmacol Ther. 2014 Aug;40[40]:382-91). Data are scarce in North America concerning asthma control and functional GI disorders in both pediatric and adult populations.

The validated Questionnaire on Pediatric Gastrointestinal Symptoms–Rome III version was used to assess functional GI disorders. Asthma control was assessed using the Childhood Asthma Control Test

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pediatric Use: Safety and effectiveness of Letairis in pediatric patients have not been established.

Geriatric Use: In the two placebo-controlled clinical studies of Letairis, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with Letairis than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

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

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

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

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

GS22-081-015-PI October 2015



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



VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: It is so important to understand what comor-

bidiities our patients may have, and this article highlights gastrointestinal concerns for our asthma patients. It is an excellent prospective study in a wide range of ages, and I hope that this research will be expanded to benefit our patients and help us to manage their health more effectively.



State e-cigarette laws linked to reduced youth use

BY TARA HAELE

Frontline Medical News

Several state regulations governing the sales or use of e-cigarettes and related products were associated with lower proportions of youth trying or regularly using vaping products, a new study found.

Restricting sales of electronic vapor products to minors, however, was not linked to a lower risk of vaping among teens.

“It may be too soon to tell if the state level restrictions are having an impact,” said lead author Sarah A. Keim, PhD, of Nationwide Children’s Hospital in Columbus, Ohio, in an interview. “However, it was reassuring to see these early indicators that they may be having an effect so early on, and so these findings were not surprising.”

Dr. Keim and her associates investigated possible associations between various state laws related to vaping products, all passed before 2015, and youth use of the products. They relied on 2015 data from 35 state-specific surveys of youth regarding use of vaping products and from the Youth Risk Behavior

Survey from the Centers for Disease Control and Prevention, a nationally representative, biannual survey of students in grades 9-12. The Tobacco Control Laws Database of the American Nonsmokers’ Rights



DR. KEIM

Foundation provided information on state laws related to electronic vapor products. Among the 200,513 teens whose responses were included in the study, 44% had ever used any kind of electronic vapor product. Rates were similar between girls and boys for ever having tried one or currently using one, Dr. Keim reported at the Pediatric Academic Societies annual meeting.

Experimentation began young for most: 35% of respondents tried an e-cigarette before age 14 years, and 18% under age 14 currently use vaping products. By age 17, half of all kids had tried an e-cigarette or related product, and a quarter were currently using them.

The researchers looked at associations with each of the following types of laws:

- Statewide prohibition of vaping products on school property or in workplaces, which includes Arizona, New Hampshire, Vermont, and Virginia for schools and North Dakota for workplaces.
- Prohibition of sales to minors under age 18 years, present in 24 states.
- Prohibition or restriction of sales of e-cigarette products from vending machines, present in 17 states.
- Prohibition or restriction of self-service displays of vaping products, present in 11 states.
- Prohibition or restriction of sampling of electronic vapor products, present in Arizona, Delaware, Kentucky, Maryland, New Hampshire, North Carolina, Oklahoma, and South Carolina.

For most of the regulations, teens had a reduced likelihood of trying or currently using vaping products after adjusting for age, ethnicity, grade level, race, region, and sex. Risk of ever trying a vaping product was 12% lower in states that prohibited their use on school grounds or in workplaces, 6% lower in states that barred sales to those under age 18, and 7% lower in states that restricted or prohibited self-service vaping displays.

The risk of youth currently using electronic vapor products was 5% lower in states with the school grounds and workplace restrictions,



©THINKSTOCK

and 13% lower in states that restricted self-service displays. Laws restricting minor sales were unrelated to the risk of current vaping among youth. Restricting vending machine sales of vaping products had no association with the risk of a teen ever trying vaping, but it was linked to a 7% lower risk of current use of the products among teens. All these associations were statistically significant based on confidence interval values.

A statistically significant risk increase in vaping use occurred for teens in states that restricted or outlawed sampling of vaping products.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This report highlights how much we need to learn about e-cigarettes and consequences for all at-risk groups, including teens. Plus, we need to learn it FAST!



Conquer the CHALLENGE.



NETWORKS CHALLENGE

Champion Lung Health.

chestfoundation.org/networkschallenge

Continued from previous page

(ACT) questionnaire, with scores exceeding 30, less than 19, and less than 14, indicating well-controlled, not well-controlled, and poorly controlled asthma, respectively. Anxiety was assessed using the Beck Anxiety Inventory, with increasing scores indicating increasing anxiety.

The 110 enrolled patients had a mean age of 10 years. Age was similar between the 18 patients with functional GI disorders – representing a prevalence rate of 16% – and the 92 without such disorders at 12 and 10 years, respectively. Those with functional GI disorders were predominantly female, compared with the patients without a functional GI disorder (72% vs. 45%; P less than .03). The GI distress in the 18 patients comprised 10 cases of abdominal pain disorders and 13 cases of upper GI tract disorders, with 3 patients having an overlap of 2-3 functional GI disorders.

Patients with functional GI disorders had a lower mean ACT score, compared with those without (12 vs. 15; $P = .03$). Functional GI disorders also were associated with higher anxiety scores (34 vs. 14; P less than .01).





Asthma control significantly predicted the presence of functional GI disorders in univariate analysis (odds ratio, 0.9; 95% confidence interval, 0.80-0.99; $P = .03$). However, this significance was lost in a multivariate analysis that adjusted for asthma control, anxiety, and sex. The multivariate analysis revealed continued significant associations between functional GI disorders and anxiety (OR, 1.1; 95% CI, 1.01-1.10; P less than .01) and female sex (OR, 3.3; 95% CI, 1.00-10.56; P less than .05).

Dr. Colman speculated that the apparent association of asthma with chronic GI distress could reflect asthma-related inflammation that exacerbates the GI disorders.

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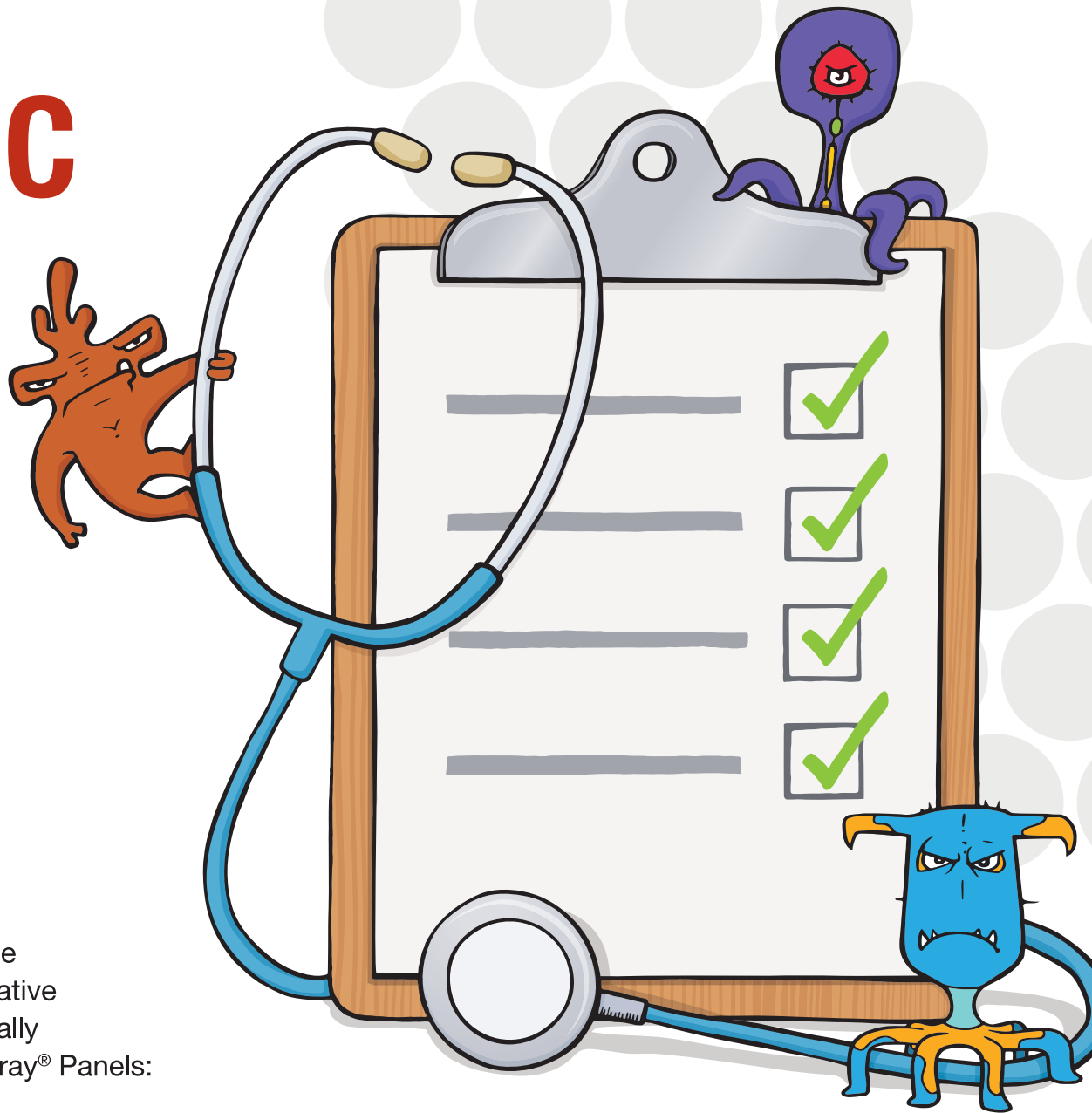
Data on file at BioFire Diagnostics.



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EHR price alert doesn't reduce lab orders

BY M. ALEXANDER OTTO

Frontline Medical News

Displaying Medicare allowable fees in the electronic health record at the time of order entry did not significantly reduce the number of inpatient lab tests at three Philadelphia hospitals.

In a study involving 98,529 patients and 142,921 admissions, Medicare payment information popped up randomly in the EHR when standard tests including complete blood cell counts, metabolic panels, and liver function tests were ordered. The costs of the labs varied depending on their extent. The message mentioned that “the dollar amount represents Medicare reimbursement for the test. Actual costs to the consumer may vary by patient insurance status.” Just over a third of the patients were actually on Medicare; most had private insurance.

The idea of the study was to see if cost information would curb unnecessary testing, and save money. “There is growing interest in using price transparency to influence medical decision making toward higher-value care,” Mina Sedrak, MD, and her colleagues said in a paper presented at the annual meeting of the Society of General Internal Medicine.

It didn't work out that way. Four tests ordered per patient-day when the messages appeared, and 2.34 when they did not. With messaging, the mean lab fee per patient-day was \$38.85, versus \$27.59 without it. In an adjusted analyses comparing the intervention to the control group,

there were no significant changes in overall test ordering (0.05 tests ordered per patient-day, $P = .06$) or associated fees when pricing information was displayed (\$0.24 per patient-day; $P = .47$).

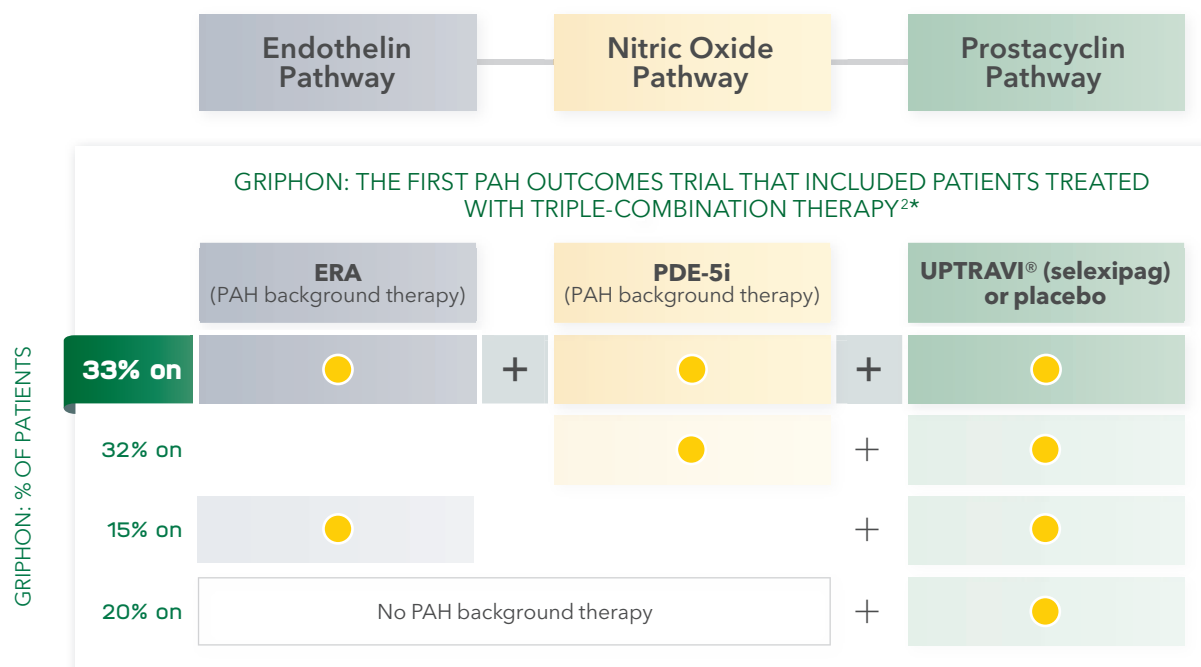
In a subset analysis, the investigators did find a small decrease in orders for the most expensive labs and a small but significant increase in orders for the least expensive ones when physicians aware of cost (top quartile

of tests based on fee value: -0.01 ; $P = .04$; bottom quartile: 0.03 , $P = .04$).

Despite the overall negative results, there's still a likely role for cost information in value improvement programs; what the study shows is that

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

Triple UP
3 Oral Therapies for 3 Pathways



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

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

INDICATION

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

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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Pulmonary Veno-Occlusive Disease (PVOD)

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

ADVERSE REACTIONS

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

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

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

DRUG INTERACTIONS

Strong CYP2C8 inhibitors

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

Please see additional Important Safety Information on adjacent page.

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

VIEW ON THE NEWS

Michael E. Nelson, MD, FCCP,

comments: One also needs

to consider the effects of information overload and alert fatigue, both of which have been well-documented since the advent of EMRs. Most interesting is the fact that knowledge of the price actually was associated with a slight increase in test ordering, although not statistically significant. It would be even more interesting to conduct a similar study providing the knowledge to both the patient and the physician.



there's a better way to use it, according to Dr. Sedrak, currently of the City of Hope Comprehensive Cancer Center in Duarte, Calif., and colleagues.

The investigators made several suggestions when reviewing their work.

"First, the price transparency intervention in this study was always displayed regardless of the clinical

scenario. The presence of this information for appropriate tests may have diminished its impact when tests were inappropriate. Future efforts may consider more selective targeting of price transparency." It might also be a good idea to price out different testing options for providers, and use actual charges and other more on-point forms of

cost estimates, they said, instead of Medicare fees that have little to do with what many patients are actually charged. Targeting only the most expensive tests might also help (JAMA Intern Med. 2017 Apr 21. doi: 10.1001/jamainternmed.2017.1144). The investigators also noticed a problem when labs are ordered to repeat automatically; clinicians did

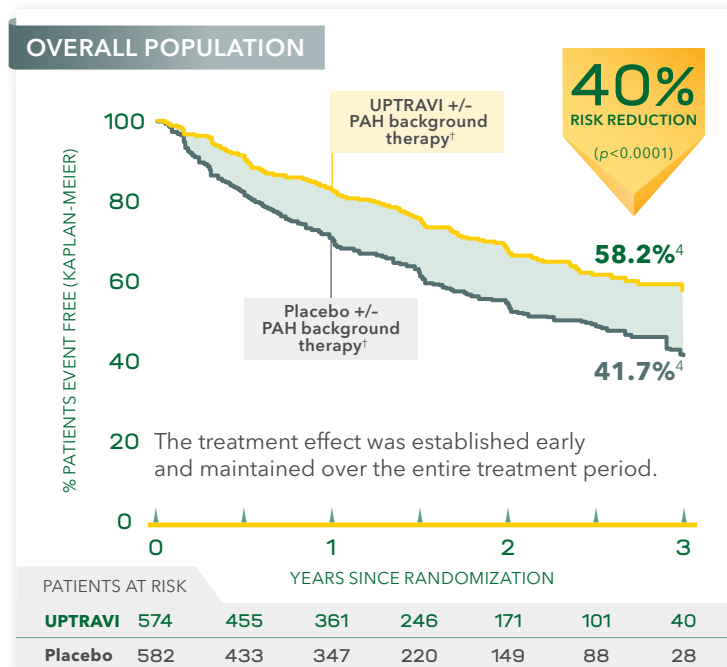
not see the price information every day, and so missed cost information "when it would be most salient."

The mean age in the study was 54.7 years; 52% of the patients were white, 39% black, and 57% women. The mean length of stay was about 6 days, and over 80% of the patients were discharged home.

aotto@frontlinemedcom.com

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

PRIMARY ENDPOINT: TIME TO FIRST DISEASE PROGRESSION EVENT IN GRIPHON



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

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

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

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

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

IMPORTANT SAFETY INFORMATION (cont'd)

DOSAGE AND ADMINISTRATION

Recommended Dosage

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

Patients with Hepatic Impairment

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

Dosage Strengths

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

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

[†]An ERA, PDE-5i, or both.

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

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

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

Visit www.UPTRAVI.com/hcp to learn more

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



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Letter to *CHEST* Leaders, Members, and Friends

Dear *CHEST* Leaders, Members, and Friends:

The Forum of International Respiratory Societies (FIRS) is an organization comprised of the world's leading international professional respiratory societies presenting a unifying voice to improve lung health globally. Its members are: the American College of Chest Physicians (CHEST), American Thoracic Society (ATS), Asian Pacific Society of Respiriology (APSR), Asociación Latinoamericana De Tórax (ALAT), European Respiratory Society (ERS), International Union Against Tuberculosis and Lung Diseases (The Union), the Pan African Thoracic Society (PATS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD), and the Global Initiative for Asthma (GINA). FIRS has more than 70,000 professional members; the physicians and patients they serve magnify our efforts, allowing FIRS to speak for lung health on a global scale.

FIRS is working with the World Health Organization and the United Nations to make sure lung health is represented in national health agendas. FIRS' position paper on electronic nicotine delivery systems was presented at a side-event at the United Nations High-Level Meeting (UNHL) in New York in 2014 and is now a world standard. At the recent World Health Assembly meeting (May 2017) in Geneva, FIRS launched its Global Impact of Lung Disease report that called for a global clean air standard, strong anti-tobacco laws, and better health care for patients with respiratory disease.

FIRS will be reviewing the new WHO Global Air Quality Guidelines and will help promote

them globally through advocacy and messaging, as well as by providing air quality expertise. FIRS will be involved at the Coimbra meeting (Sept 26-29) on improving the urban environment, the Montevideo UN High-Level (UNHL) meeting on chronic disease (Oct 18-20), and the UN Ministerial Meeting in Moscow on tuberculosis, and it is preparing for the 2018 UNHL meetings on antibiotic drug resistance, tuberculosis, and chronic diseases.

At the World Health Assembly, FIRS proclaimed September 25 as World Lung Day and hopes to use this as a rallying point for advocacy related to respiratory health or air quality. Lung Disease is the only major chronic disease that does not have a World Day. FIRS produced a Charter for Lung Health (www.firsnet.org/publications/charter) and hopes to have 100,000 persons sign on to it. FIRS also seeks to have lung-health organizations sign on and develop activities that can be carried out to celebrate lung health. Uruguay was the first country to sign the charter. The logos of the organizations who have signed the charter are on the FIRS website at firsnet.org. Activities being planned include editorials, newsletters, and letters-to-the-editor articles, legislative proclamations, social media exposure, and free spirometry, smoking cessation guidance, and carbon monoxide testing, but FIRS is looking for many more ways to celebrate healthy lungs on September 25 and many more partners!

Sixty-five million people suffer from chronic obstructive pulmonary disease and 3 million die of it each year, making it the third leading cause of death worldwide; 10 million people develop tuberculosis and 1.4 million die of it each year, making

it the most common deadly infectious disease; 1.6 million people die of lung cancer each year, making it the most deadly cancer; 334 million people suffer from asthma, making it the most common chronic disease of childhood; pneumonia kills millions of people each year, making it a leading cause of death in the very young and very old. At least 2 billion people are exposed to toxic indoor smoke; 1 billion inhale polluted outdoor air; and 1 billion are exposed to tobacco smoke, and the tragedy is that many conditions are getting worse. We cannot sit still and allow this to happen.

FIRS proposes a multipronged campaign to combat lung disease to bring together all people concerned with lung health. It starts with naming September 25 World Lung Day and calling on respiratory health organizations to pledge to improve lung health and help identify ways to celebrate this day.

Please sign up, and share this call for action with your professional, advocacy, and social networks, and those of your friends and families. Please do your part as global citizens to improve lung health. To do so, organizations should indicate they wish to sign on and send their logo to Betty Sax, FIRS Secretariat, betty.sax@ersnet.org. Organizations should also encourage individuals to sign on and show that they are committed to increasing awareness and action to promote global lung health.

Thank you.

Gerard Silvestri, MD, MS, FCCP
CHEST President
Darcy Marciniuk, MD, FCCP
CHEST FIRS Liaison



CHEST[®] journal — new online home

We are excited to share that the journal *CHEST*[®] has a new website with improved navigation, better search capabilities, alert sign-ups, and more multimedia elements. We are asking members to take a few minutes to activate their new account.

In order to maintain continuous access to the online journal, members will have to register for a free account and claim their subscription. If you go to chestjournal.org, CHEST members can then complete a 1- to 2-minute registration process.

"This is an exciting time for the journal, and I personally believe that online users will be very pleased with what the new



web version has to offer," says Dr. Richard Irwin, *CHEST*'s Editor in Chief.

CHEST members should have received an email with step-by-step instructions. Still have questions or need help? Contact Online Journal Support at 800/654-2452 (US and Canada) or +44 (0) 1865-843177 (Europe).

This Month in *CHEST*: Editor's picks

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

GIANTS IN CHEST MEDICINE:
Steven E. Weinberger, MD, FCCP
By Dr. J. Mandel

EDITORIAL
Precision Medicine Urgency:
The Case of Inhaled
Corticosteroids in COPD
By Drs. S. Suissa and P. Ernst

ORIGINAL RESEARCH
Physician Assessment
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Malignancy and Adherence
With Guidelines for Pulmonary
Nodule Evaluation
By Dr. N. T. Tanner, et al.

The Long-Term Effect of Bacille
Calmette-Guérin Vaccination on
Tuberculin Skin Testing: A 55-



Year Follow-Up Study
By Dr. J. D. Mancuso, et al.

Clinical Characteristics of
Pertussis-Associated Cough
in Adults and Children: A
Diagnostic Systematic Review
and Meta-Analysis
By Dr. A. Moore, et al.

For appropriate patients with DVT/PE

Choose ELIQUIS from the **START**



DVT: deep vein thrombosis; PE: pulmonary embolism.

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

Eliquis[®]
(apixaban) tablets 5mg
2.5mg

ELIQUIS for initial DVT/PE treatment*—

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



To learn more about ELIQUIS, visit

hcp.eliquis.com



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

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

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

PREGNANCY CATEGORY B

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

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

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

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Bristol-Myers Squibb



CHEST Membership News

We're Rewarding You

Introducing CHEST Participation Points

Everyday, you commit your time to helping patients. We recognize your dedication not only to your profession but to the CHEST community.

We're happy to introduce CHEST Participation Points, designed to increase member recognition and reward you for participating and

contributing to our diverse community. Wherever you are in your career, you can earn points for the things you do within the CHEST community.

Members can now earn 10, 20, or 30 points for participating in eligible activities such as attending CHEST Annual Meeting, submitting abstracts, participating in a CHEST Twitter chat, becoming a Fellow of

the American College of Chest Physicians (FCCP), and more!

Once you receive 50, 100, or 150 points, you can redeem your points for CHEST-branded apparel or discounts on courses and products.

Point accrual started on July 5, so you've already been earning points. If you are an FCCP, you began with 30 points awarded for becoming FCCP—that's only 20 points away

from the first tier of prizes. To accrue or redeem points, you must be an active member and current with your dues.

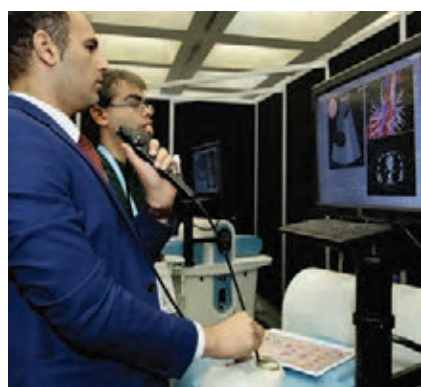
Log in to your CHEST account, and access Participation Points in the left column to see your points.

Start earning more points today! Learn more at chestnet.org/participationpoints.

10 Points	20 Points	30 Points
Complete a short survey	Refer a member	Become an FCCP
Join a new NetWork	Serve as a moderator	Donate to the CHEST Foundation
Participate in a Twitter chat	Attend a live course	Submit a topic for CHEST Annual Meeting
Attend a networking event	Complete a long survey	Attend 5 consecutive CHEST Annual Meetings
Volunteer in CHEST booth	First time membership renewal	Participate in a focus group, work group, or ad hoc committee
Attend CHEST Annual Meeting	Attend 3 consecutive CHEST Annual Meetings	Submit an abstract or case report for CHEST Annual Meeting
Serve as abstract/case report grader for CHEST Annual Meeting	Participate in a CHEST webinar	Participate in a community service event
		Participate in the mentorship program

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Comprehensive Bronchoscopy With Endobronchial Ultrasound

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Vaccination: An Important Step in Protecting Health

Patients with chronic lung conditions, like COPD and asthma, need to take extra steps to manage their condition and ensure the healthiest possible future. One important step that may not always be top of mind is vaccination, which can protect against common preventable diseases that may be very serious for those with respiratory conditions. CDC recommends adults with COPD, asthma, and other lung diseases get an annual flu vaccine, as well as stay up to date with pneumococcal and other recommended vaccines. Additional vaccines may be indicated based on age, job, travel locations, and lifestyle.

COPD and asthma cause airways to swell and become blocked with mucus, making it hard to breathe. Certain vaccine-preventable diseases can make this even worse. Adults with COPD and asthma are at increased risk of complications from influenza, including pneumonia and hospitalization. They are also at higher risk for invasive

pneumococcal disease and more likely to develop infections including bacteremia and meningitis. Each year, thousands of adults needlessly suffer, are hospitalized,

One important step that may not always be top of mind is vaccination, which can protect against common preventable diseases that may be very serious for those with respiratory conditions.

and even die of diseases that could be prevented by vaccines. Despite increased risks, less than half of adults under 65 years with COPD and asthma have received influenza and pneumococcal vaccination (National Health Information Survey 2015).

Find the latest recommended adult immunization schedule at www.cdc.gov/vaccines/hcp/adults.

CRITICAL CARE COMMENTARY

Conscience Rights, Medical Training, and Critical Care

A Medical Student Perspective

BY ANA-MARIA DUMITRU, PHD; BENJAMIN W. FRUSH, MA; CHRIS RADLICZ, MS, MPH; PHILIP ALLEN, BS; MARTIN T. BROWN, BS; JEREMY BANNON, BSC; AND JOHN Y. RHEE, MPH

“No provision in our Constitution ought to be dearer to man than that which protects the rights of conscience against the enterprises of the civil authority.”— Thomas Jefferson (Washington HA. The Writings of Thomas Jefferson. New York: Biker, Thorne, & Co. 1854; Vol 3:147.)

What is the proper role of conscience in medicine? A recent article in the New England Journal of Medicine (Stahl & Emmanuel. *N Engl J Med.* 2017; 376(14):1380) is the latest to address this question. It is often argued that physicians who cite conscience in refusing to perform requested procedures or treatments necessarily in-

fringe upon patients' rights. However, we feel that these concerns stem from a fundamental misunderstanding of what conscience is, why it ought to

be respected as an indispensable part of medical judgment (Genius & Lipp. *Int J Family Med.* 2013; Epub 2013 Dec 12), and how conscience is ori-

ented toward the end goal of health, which we pursue in medicine.

By failing to define “conscience,”

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EDITOR'S NOTE:

When I invited Dr. Wes Ely – the coauthor of a recent article regarding physician-assisted suicide – to write a Critical Care Commentary on said topic, an interesting thing happened: he declined and suggested that I invite a group of students from medical schools across the country to write the piece instead. The idea was brilliant, and the resulting piece was so insightful that the CHEST® journal editorial leadership suggested submission to the journal, and the accepted article will appear in the September issue. Out of that effort, the idea for the present piece was born. The result is an opportunity to hear the students' voices, not only to stimulate discussion on conscientious objection in medicine but also to remind the ICU community that our learners have their own opinions and that through dialogues such as this, we might all learn from one another.

Lee Morrow, MD, FCCP

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Indication

UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate) is a combination of indacaterol and glycopyrrolate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important limitations: UTIBRON NEOHALER is not indicated to treat acute deteriorations of COPD and is not indicated to treat asthma.

Important Safety Information



WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including indacaterol, one of the active ingredients in UTIBRON NEOHALER.

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

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

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

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the crux of the argument against conscience rights is built on the basis of an implied diminution of conscience from an imperative moral judgment down to mere personal preference. If conscience represents only personal preference – if it is limited to a set of

choices of the same moral equivalent as the selection of an ice cream flavor, with no need for technical expertise—then it would follow that

Conscience ought to be respected as an indispensable part of medical judgment.

a physician ought to simply comply with the patient's decisions in any given medical situation. However, we know intuitively that this line of

reasoning cannot hold, if followed to its conclusion. For example, if a patient presenting with symptoms of clear rhinorrhea and dry cough in December asks for an antibiotic, through this patient-sovereignty model, the physician surely ought to provide the prescription to honor the

UTIBRON™ NEOHALER®
(indacaterol/glycopyrrolate) inhalation powder

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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

INDICATIONS AND USAGE: UTIBRON™ NEOHALER® is a combination of indacaterol and glycopyrrolate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: UTIBRON NEOHALER is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

CONTRAINDICATIONS: UTIBRON NEOHALER is contraindicated in patients with asthma without use of a long-term asthma control medication. UTIBRON NEOHALER is contraindicated in patients who have demonstrated hypersensitivity to indacaterol, glycopyrrolate, or to any of the ingredients.

WARNINGS AND PRECAUTIONS:

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

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

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

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

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

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

patient's request. The patient would have every right to insist on the antibiotic, and the physician would be obliged to prescribe accordingly. We, as students, are trained, however, that it would be morally and professionally fitting, even obligatory, for the physician to refuse this request,

precisely through exercise of his/her professional conscience.

If conscience, then, is not simply a subject of one's personal preferences, how are we to properly understand it? Conscience is "a person's moral sense of right and wrong, viewed as acting as a guide to one's behavior"

(Conscience. Oxford Dictionary. Oxford, Oxford University Press. 2017). It exhibits the commitment to engage in a "self-conscience activity, integrating reason, emotion, and will, in self-committed decisions about right and wrong, good and evil" (Sulmasy. *Theor Med Bioeth.*

2008; 29(3):135). Whether or not a person intentionally seeks to form his/her conscience, it continues to be molded through the regular actions of daily life. The actions we perform – and those we omit – constantly shape our individual consciences. One's conscience can indeed err due to emotional imbalance or faulty reasoning, but, even in these instances, it is essential to invest in the proper shaping of conscience in accordance with truth and goodness, rather than to reject the place of conscience altogether.

By attributing appropriate value to an individual's conscience, we thereby recognize the centrality of conscience to identity and personal integrity. Consequently, we see that forcing an individual to impinge on his/her conscience through coercive

The actions we perform – and those we omit – constantly shape our individual consciences.

means incidentally violates that person's autonomy and dignity as a human being capable of moral decision-making.

In the practice of medicine, the free exercise of conscience is especially relevant. When patients and physicians meet to act in the pursuit of the patient's health, they begin the process of conscience-mediated shared decision-making, rife with the potential for disagreement. Throughout this process, a physician should not violate a patient's conscience rights by forcing medical treatment where it is unwanted, but neither should a patient violate a physician's conscience rights by demanding a procedure or treatment that the physician cannot perform in good conscience. Moreover, to insert an external arbiter (eg, a professional society) to resolve the situation by means of contradiction of conscience would have the same violating effect on one or both parties.

One common debate as to the application of conscience in the setting of critical care focuses on the issue of physician-assisted suicide and euthanasia (PAS/E) (Rhee J, et al. *Chest.* 2017;152[3]. Accepted for Sept 2017 publication). Those who would deny physicians the right to conscientiously object to PAS/E depict this as merely an issue of the physician's personal preference. Given the distinction between pref-

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

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

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

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


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

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



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

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

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

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Continued from previous page

erence and conscience, however, we recognize that much more is at play. For students and practitioners who hold that health signifies the “well-working of the organism as a whole,” (Kass L. *Public Interest*. 1975; 40(summer):11-42) and feel that the killing of a patient is an action that goes directly against the health of the patient, the obligation to participate in PAS/E represents not only a violation of our decision-making dignity, but also subverts the critical component of clinical judgment inherent to our profession. The conscientiously practicing doctor who follows what they believe to be their professional obligations, acting in accordance with the health of the patient, may reasonably conclude that PAS/E directly contradicts their obligations to pursue the best health interests of the patient. As such, their refusal to participate can hardly be deemed a simple personal preference, as the refusal is both reasoned and reasonable. Indeed, experts have concluded that regardless of the legality of PAS/E, physicians must be allowed to conscientiously object to participate (Goligher et al. *Crit Care Med*. 2017; 45(2):149).

As medical students who have recently gone through the arduous medical school application process, we are particularly concerned with the claim that if one sees fit to exercise conscientious objection as a practitioner, they should leave medicine, or choose a field in medicine with few ethical dilemmas. To crassly exclude students from the pursuit of medicine on the basis of the shape of their conscience would be to unjustly discriminate by assigning different values to genuinely held beliefs. A direct consequence of this exclusion would be to decrease the diversity of thought, which is central to medical innovation and medical progress. History has taught us that the frontiers of medical advancement are most ardently pursued by those who think deeply and then dare to act creatively, seeking to bring to fruition what others deemed impossible. Without conscience rights, physicians are not free to think for themselves. We find it hard to believe that many physicians would feel comfortable jettisoning conscience in all instances where it may go against the wishes of their patients or the consensus opinion of the profession.

Furthermore, as medical students, we are acutely aware of the importance of conscientious objection due to the extant hierarchical nature of

medical training. Evaluations are often performed by residents and physicians in places of authority, so students will readily subjugate everything from bodily needs to conscience in order to appease their attending physicians. Evidence indicates that medical students will even fail to object when

they recognize medical errors performed by their superiors (Madigosky WS, et al. *Acad Med*. 2006; 81(1):94).

It is, therefore, crucial to the proper formation of medical students that our exercise of conscience be safeguarded during our training. A student who is free to exercise conscience

is a student who is learning to think independently, as well as to shoulder the responsibility that comes as a consequence of free choices.

Ultimately, we must ask ourselves: how is the role of the physician altered if we choose to minimize the role of conscience in medicine? And

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

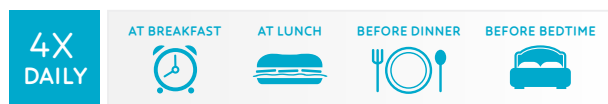
GO WITH TYVASO: a direct-to-the-lungs



Increase efficacy with Tyvaso (treprostinil) when added to oral monotherapy¹

- + Adding Tyvaso increased median 6MWD by 20 m ($P < 0.001$) after 1.7 years (mean) on background therapy (sildenafil or bosentan)^{1,2}
- + Tyvaso was studied in TRIUMPH I, a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for ≥ 3 months before study initiation^{1,2}
- + Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) over the course of the 12-week study^{1,2}

Tyvaso can fit into their daily routine¹



- + Treatment sessions of ~2 to 3 minutes in length can be scheduled during waking hours and around daily activities, approximately every 4 hours^{1,3}
- + Dosing should be titrated to the target dose of 9 breaths, 4x daily¹
- + Begin with 3 breaths per treatment session, and increase by 3 breaths per session at 1- to 2-week intervals¹
- + The most common adverse events included cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope¹

INDICATION

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

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

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

6MWD=6-minute walk distance; NYHA=New York Heart Association; TRIUMPH=TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension; WHO=World Health Organization.

References: 1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2014. 2. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922. 3. Tyvaso [patient prescribing information]. Research Triangle Park, NC: United Therapeutics Corporation; 2013.

do patients truly want physicians who forfeit their consciences even in matters of life and death? If we take the demands of those who dismiss conscience to their end – that only those willing to put their conscience aside should enter medicine – we would be left with practitioners

whose group think training would stifle discussion between physicians and patients, and whose role would be reduced to simply acquiescing to any and all demands of the patient, even to their own detriment. Such a group of people, in our view, would fail to be physicians.

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sicians and Surgeons, New York, NY (Mr. Allen); Thomas Jefferson School of Medicine, Philadelphia, PA (Mr. Brown); Faculty of Medicine & Dentistry, University of Alberta School, Edmonton, AB, Canada (Mr. Bannon); Icahn School of Medicine at Mount Sinai, New York, NY (Mr. Rhee).

prostacyclin analogue¹



IMPORTANT SAFETY INFORMATION FOR TYVASO WARNINGS AND PRECAUTIONS

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

DRUG INTERACTIONS / SPECIFIC POPULATIONS

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

ADVERSE REACTIONS

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

TYVSIhpcJUN16

Please see Brief Summary of Full Prescribing Information.

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

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PULMONARY PERSPECTIVES®

Immigrants in Health Care

July 4th was bittersweet for me, this year. Independence days of my childhood were spent grilling, sitting by the campfire on the

lakes and rivers of Northern Michigan, watching the fireworks turn the night sky red, white, and blue. These fond memories were a painful

reminder that others like me may not have the privilege to experience such joy, secondary to their background.

BY NITIN PURI, MD, FCCP
Pulmonary Perspectives Section Editor

I don't remember the first time that I heard the tale of my parents coming to America. They were both medical students from India, who received brightly colored brochures from American hospitals inviting them to come further their medical training. Due to the deficit of physicians in the United States, the hospitals even loaned money to medical students, so they would do their residencies in America. My parents took advantage of this opportunity and embarked on a journey that would define their lives. Often, my mother would talk about my father leaving for the hospital on Friday morning only to return to his wife and two toddlers on Monday afternoon. As a child, I remember my uncles taking bottles of milk to the hospital to make chai to fuel through their grueling overnight calls. These immigrant tales were the backdrop of my childhood, the basis of my understanding of America. I was raised in an immigrant community of physicians who were grateful for the opportunities that America offered them. They worked hard, reaped significant rewards, and substantially contributed to their communities. Maybe, I am just nostalgic for my childhood, but this experience, I believe, is still an integral part of the American dream.

The recent choice to restrict immigration from specific nations is disturbing at best and reminiscent of an America that I have never known. More than 7,000 physicians from Libya, Iran, Somalia, Sudan, Syria, and Yemen are currently working in the United States, providing care for more than 14 million people. An estimated 94% of American communities have at least one doctor from one of the targeted countries. These physicians are more likely to work in rural and underserved communities and provide essential services.¹ They are immigrants who have come to America to better their lives and, in turn, have bettered the lives of those around them. They are my parents. Not all physicians are good people or are worthy of the American dream, but America is a better place for welcoming those who are willing to work hard to make a better life for themselves. An important criticism of the effect of migration of medical professionals to the United



BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

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

ADVERSE REACTIONS

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

- Decrease in systemic blood pressure
- Bleeding

Adverse Reactions Identified in Clinical Trials—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache; gastrointestinal effects; muscle, jaw, or bone pain; flushing; and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

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

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

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

*More than 3% greater than placebo

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

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

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

DRUG INTERACTIONS

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

OVERDOSAGE

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

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



States has been the loss of human capital to their respective nations, but never the ill-effect they have had on the nations they have emigrated to.

The 2015 Educational Commission for Foreign Medical Graduates (ECFMG) reported that a quarter of practicing physicians in the United States are international medical graduates (IMGs) and a fifth of all residency applicants were IMGs.² Measuring the impact of the IMGs who have come to America is difficult to quantify but can be assessed by countless anecdotes and success stories. Forty-two percent of researchers at the seven top cancer research centers in the United States are immigrants. This is impressive considering that only about a tenth of the United States population is foreign born. Twenty-eight American Nobel prize winners in Medicine since 1960 are immigrants and taking a broader view as seen in Figure 1, almost 28% of physicians and 22% of RNs in the United States are foreign born.^{3,4} That does not take into account those like myself, first generation children who chose to enter this field of work out of respect for what their parents had accomplished.

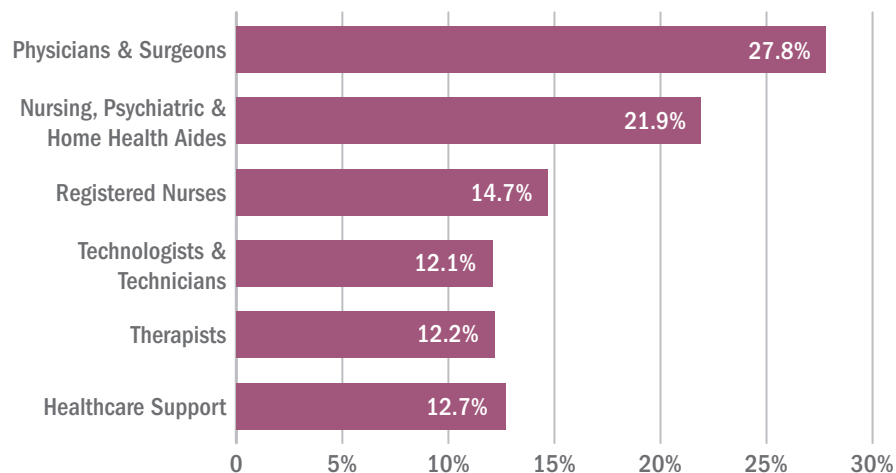
The American College of Chest Physicians (CHEST), over the past

15 years, has had several Presidents who are American immigrants. One of them, Dr. Kalpalatha K. Guntupalli, President 2009-2010, I have met, and I was humbled by the experience. She is brilliant, kind, and modest and without her knowing, she has served as one of the role models for my career.

I applaud CHEST for standing with other member organizations to oppose the immigration hiatus (Letter to John F. Kelly, Secretary of Homeland Security, Feb 7, 2017). The medical organizations made four concrete proposals:

- Reinstate the Visa Interview Waiver Program, as the suspension of this program increases the risk for significant delays in new and renewal visa processing for trainees from any foreign country;
- Remove entry restrictions of physicians and medical students from the seven designated countries that have been approved for J-1, H-1B or F-1 visas;
- Allow affected physicians to obtain travel visas to visit the United States for medical conferences, as well as other medical and research related events; and
- Prioritize the admission of refugees with urgent medical needs who had

FIGURE 1
Foreign-Born Share of Healthcare Workers by Occupation, 2010



Source: Adapted from American Community Survey 5-year estimates (2010-2014) and IPUMS-USA, University of Minnesota, www.ipums.org.

already been checked and approved for entry prior to the executive order.

These recommendations were good but not broad enough. The decision to bar immigration for any period of time, from any country, is an affront to the American dream with long-lasting consequences, most importantly, the loss of healthcare services to the American populace. My Congressman knows how I feel about this, does yours?

1. [Fivethirtyeight.com/features/trumps-new-travel-ban-could-affect-doctors-especially-in-the-rust-belt-and-appalachia/](http://fivethirtyeight.com/features/trumps-new-travel-ban-could-affect-doctors-especially-in-the-rust-belt-and-appalachia/). Accessed July 18, 2017.

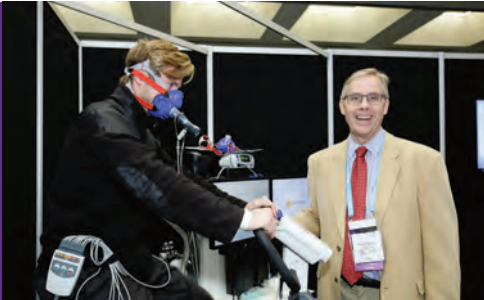
2. Masri A, Senussi MH. Trump's executive order on immigration—detrimental effects on medical training and health care. *N Engl J Med*. 2017; 376(19): e39.

3. <http://www.immigrationresearch-info.org/report/immigrant-learning-center-inc/immigrants-health-care-keeping-americans-healthy-through-care-a>. Accessed July 27, 2017.

4. <http://www.nfap.com/wp-content/uploads/2015/05/International-Educator.May-June-2015.pdf>. Accessed July 27, 2017 (not available on Safari).

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Catching Up With Our CHEST Past Presidents

Where are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians, leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's strategic initiatives. Let's check in with Dr. Goldberg.

ALLEN I. GOLDBERG, MD, MASTER FCCP

President 1998-1999

I arrived in Toronto in 1998 to start my term as President of the American College of Chest Physicians. (I had always loved Toronto, where I had spent months training in pediatric critical care at "Sick Kids" [Toronto's Children's Hospital] and collaborating with Audrey King on disability issues and public policy in Ontario.) CHEST 1998 in Toronto was equally exciting. What I remember - with humility - was that being CHEST President is not about "you." It is about "The President," who is honored and revered by all members for what CHEST truly

represents ... excellence in health-care education, communication, and information. Everyone came up to me to respect and honor the role ... including awesome Past Presidents who lovingly shared their insights and experience and others (including many who became future presidents) to volunteer their assistance. I was in awe of these leaders and how they demonstrated selfless service.

And so I began my year of presidential service leadership. What I remember best is the respect all around the world for CHEST and what it does to unite people into actions that improve health globally. The President serves CHEST members to facilitate working together, which makes a difference. My presidential year culminated in the 65th anniversary conference in Chicago in 1999. All year, I had worked with my mentor (C. Everett Koop, MD, FCCP(Hon), to plan an opening ceremony that would be inspirational and unforgettable. For years, we had shared personal/private conversations. This time, we planned to communicate in public to inspire others and help them understand key issues



Dr. Koop presided over a student competition to design innovations in communication of information about asthma. This event was held at Northwestern-Kellogg School of Management, sponsored by the CHEST Foundation (Dr. Goldberg far right).

we considered critical for the future of health care and global health.

Soon after my Presidential term, I took 2 years off for sabbatical to work more closely with Dr. Koop (2000-2002). Then, I retired to continue to focus on our work together and as personal caregiver for my wife, Evi Faure, MD, FCCP. Dr. Koop and I met many times and also held more public presentations, including the 2003 Surgeons' General National Meeting on Overcoming Health Disparities at Howard University arranged with CHEST Past President Dr. Alvin Thomas.

All our joint efforts focused on the importance of **Communication in Health Care**. We shared the belief that communication of health information would create the "informed patient and family" who would then work together in partnership with health-care professional team members. We thought that this would be the best way to improve and reform health-care delivery. We sought to provide information (the "what") in

ways that it would be trusted, understandable, and easily usable (the "how") for patients and families (the "who"). Our goal was to use evolving digital technology and personal health communicators who would facilitate information exchange. This would enable patients/families to make decisions and take actions to manage their health and identify and obtain the resources they needed (the "why") at times of need (the "when"). This concept was built on our long-term shared commitment and belief in patient self-help and self-management.

My greatest learning was the importance of mentorship - both for the mentor and mentee. This fosters communication that enables learning and growth in our abilities to serve others by the profession we love.

<http://www.chestnet.org/News/Blogs/CHEST-Thought-Leaders/2013/06/Dr-Koops-Legacy-Reflections-on-Mentorship>

<http://www.chestnet.org/News/Blogs/CHEST-Thought-Leaders/2013/08/The-Legacy-of-Dr-Koop-Reflections-on-Our-Fireside-Chat>



Dr. Allen I. Goldberg (left) attends Dr. C. Everett Koop's wedding and congratulates him on his marriage. "Dr. Koop was remarried at age 94. I was delighted to attend this special event," Dr. Goldberg said.

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CHEST Joint Congress in Basel, Switzerland

Members of CHEST leadership, faculty, and staff traveled to Basel, Switzerland, in June, to participate in the CHEST Joint Congress, which was co-hosted with the Swiss Respiratory Society, Schweizerische Gesellschaft Fur Pneumologie (SPG). Overall, there were approximately 1,100 total attendees, representing over 40 countries, who enjoyed the scientific program and gained valuable chest medicine knowledge. Among the many topics presented were diagnosis and treatment of ILD; biologics for severe asthma; EBUS for molecular analysis; and ICS in COPD. Plus, hands-on, interactive workshops were offered for learning or reviewing more procedural skills. We invite you to view webcasts of five of the Basel sessions at bit.ly/chestsgp2017.

The CHEST Joint Congress in Basel represented the second collabo-



CHEST President, Gerard Silvestri, MD, FCCP, at the CHEST booth in Basel.

rative scientific conference endeavor with a third party, the first being the CHEST Conference held in Amsterdam May 6-9, COPD: Current Excellence and Future Development.

New Tools in Campaign to Fight Asthma

The Allergy & Asthma NetWork, the nation's leading patient education and advocacy organization for people with allergy and asthma, has once again joined forces with the CHEST Foundation in an effort to empower patients suffering from severe asthma.

The campaign's focus is to educate health-care providers, patients, parents of asthmatics, and the public about the most current treatment options for asthma, highlight the importance of referring to specialists to improve patient outcomes, and bring to light the role of the entire health-care team in the care of a patient with severe or difficult-to-control asthma.

This is the second year of this growing campaign, and there are several new and exciting materials.

Severity Assessment Tool

Available online and in print, the severity assessment tool was designed to help a patient, and the clinician, understand the severity of their asthma. Not only does the tool evaluate the severity of their condition, but it also helps the patient

become more aware of their symptoms.

The seven-question assessment includes questions on usage of

quick-relief or rescue inhalers, visits to the ED/hospital, physical activity, controller medication, and quality of sleep.

Patient and Caregiver Testimonials

The campaign features several patient and caregiver testimonials that tell the stories of patients and

Continued on following page



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Please reply with CV to

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Minneapolis, Minnesota 55407

Fax: 612-871-4883 or by email to

dh@mlc-msi.com
www.minnlung.com



Pulmonary/Critical Care with Sleep Cambridge Health Alliance • Cambridge, MA

Cambridge Health Alliance (CHA) an award-winning public healthcare system, has an opportunity for a Pulmonary/ Critical Care Physician to join our existing Pulmonary team. Our system is comprised of three hospital campuses and an integrated network of both primary and specialty care practices in the Boston area. CHA is a teaching affiliate of both Harvard Medical School (HMS) and Tufts University School of Medicine.

Candidate will practice Pulmonary/CC medicine and ideally incorporate dedicated Sleep Medicine time, as well as possess a strong interest in resident and medical student teaching. Incoming physician should possess excellent clinical/communication skills and a strong commitment to serve our multicultural safety net patient population. This position has both inpatient and outpatient responsibilities. We offer a supportive and collegial environment with a strong infrastructure, inclusive of an electronic medical records system (EPIC). Candidates will have the opportunity to work in a team environment with dedicated colleagues similarly committed to providing high quality healthcare. Our employees receive competitive salary and excellent benefits.

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NETWORKS

Health-care weaponization, PTSD, depression in caregivers

Disaster Response

The tragic weaponization of health care

The Syrian conflict has highlighted the dangers to health-care workers (HCWs) in humanitarian crises. The Lancet-American University of Bei-



DR. MISHRA



DR. MAVES

rut Commission on Syria reports on the weaponization of health care in Syria – a strategy of depriving people of their health-care needs. Targeting of HCWs was recognized early in the Syrian war with targeting of health-care facilities being frequently reported throughout the conflict. HCWs facing extreme supply shortages have been reported to resort to desperate measures: using urine bags with added anticoagulants for blood collection and crafting homemade external fixators for fractures. Sadly, the Syrian conflict is not unique. The International Committee of the Red Cross (ICRC) documented 2,398 episodes of violence directed at health facilities in 11 countries affected by armed conflict between 2012 and 2014 alone. In Syria and elsewhere, the exodus of trained medical personnel, due to lack of medical training in trauma, emergency medicine, and intensive care, puts populations at further risk in

these regions. The International Red Cross and Red Crescent Movement has started the Health Care in Danger (<http://http://healthcareindanger.org>) initiative to highlight this weaponization of health, supporting efforts by HCWs to advocate for their rights and their patients' rights at a global level. This highlights the needs for CHEST members responding to humanitarian crises to ensure they have appropriate training to work in these environments and deploy with an organization that can provide adequate safeguards.

Dr. Maves is a military service member. The opinions expressed herein are his own and do not necessarily reflect the official opinions of the Department of the Navy, Department of Defense, or the US Government.

*Rashmi Mishra, MD
Fellow-in-Training Member
Ryan Maves, MD, FCCP
Steering Committee Member*

Practice Operations

The House AHCA /Senate BCRA compared with ACA (Affordable Care Act)

Health-care costs are a fundamental driver of insurance costs, which leads to challenges to coverage affordability for millions of families. There is ongoing debate whether the current law (Affordable Care Act [ACA/Obamacare]) and the republican alternatives (American Healthcare Act [AHCA] and Better Care Reconciliation Act [BCRA]) do enough to address the cost challenges. Here is a brief summary of the key similarities and differences.

Similarities: (1) Children will be

covered up to age 26. (2) Coverage of pre-existing conditions continues (high risk pools will be subsidized by a state government but premiums are up to twice as much as individual coverage). (3) Tax credit (based on age and family size rather than income level). (4) Insurance can charge older customers more than younger (up to 3X under ACA, 5X under AHCA/BCRA). (5) No annual or lifetime payout limit (but



DR. BASSILY-MARCUS

states may apply waivers allowing insurers to apply limits). **Differences:** (1) Insurance will no longer be mandatory (no individual or employer mandates, but there is a 30% increase in premiums for 1 year for not maintaining individual continuous coverage). (2) Medicaid expansion (expanded under ACA to 133% of poverty level income) will stop in 2020. (3) Restriction on "Abortion Funding" (any facility that offers abortion will not receive federal funding) for 1 year. (4) Taxes on health care will be removed (including taxes on prescription drugs, OTC, premiums, and medical devices). (5) Allowing policies for major illness or injury (with elimination of the requirement to cover ten essential health benefits, allowing states to modify).

Health-care reform undoubtedly is complicated, and there are a lot of questions in the air about the future of health care under the Trump Administration. Few certainties: change

is coming, MACRA is here to stay.

*Adel Bassily-Marcus, MD, FCCP
NetWork Chair*

Transplant

Posttraumatic Stress Disorder Post-Lung Transplant

The majority of transplant physicians are mainly concerned with issues posttransplant that are focused on the graft function. But recently, neurocognition and posttransplant posttraumatic stress disorder have been found to have significant impact on quality of life and mortality after transplantation. Posttraumatic stress disorder (PTSD) is described as re-experiencing a traumatic event in addition to having avoidant and hyperarousal symptoms, which last for a period of at least 1 month. Studies of PTSD in solid organ transplant recipients have revealed a significantly higher prevalence of PTSD symptoms (10% to 17%) compared with the general population (prevalence of 3.5% to 6%). In one study of heart transplant recipients, patients who met the criteria for PTSD in the first year posttransplant had a higher risk for 3-year mortality (OR=13.74) [Dew et al. *J Heart Lung Transplant*. 1999;18[6]:549-562].

Lung transplant recipients are at a high risk for developing PTSD due to exposure to several traumatic events, such as a life-threatening exacerbation of the underlying lung disease, undergoing transplant surgery, intensive care unit stay, delirium and episodes of infection, and acute and chronic rejection. However, data regarding the prevalence and risk factors for PTSD post-lung transplant are limited.

The prevalence of PTSD post lung transplantation has been reported to

Continued from previous page

parents of children with severe asthma.

"What we want people to understand, is that at the time of Ben's passing, he was on a preventive med. He was going to the doctor routinely. We had actually just been to the asthma doctor. We were seeing somebody, had an action plan, and everybody knew what they had to do. Even with all of that, it still came to this. Benjamin still lost his life, and we never knew this was something that could happen," stated Cristin Buckley, mother of Benjamin Buckley who was 7 years old at the time of his death. These testimonial videos will be used to raise awareness of the condition, and the importance of managing and monitoring symptoms.

Shared Decision Making Tool

The American College of Allergy, Asthma, and



Immunology (ACAAI), the Allergy & Asthma Network, and CHEST Foundation have partnered to develop a shared decision-making tool for adults with severe asthma. This tool will be launched at CHEST 2017 in October. Available online and in print, it was created for patients and clinicians to work together to improve

self-management skills, choose the best treatment plan for the patient, and increase adherence. This patient-centered approach in clinical settings improves patient satisfaction of care and overall outcomes.

Thank You to Our Supporters

The CHEST Foundation and Allergy and Asthma Network would like to thank our generous supporters, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis for making this campaign possible. It is through supporters, who are active participants in helping grow this campaign, that these important materials are able to have an impact on patient outcomes and create long-lasting social change.

To view the campaign materials, visit us at asthma.chestnet.org.

be 12.6% to 15.8%. In lung transplant recipients with clinically significant PTSD symptomatology; the presence of symptoms of re-experiencing (29.5%) and arousal (33.8%) were more common than avoidant symptoms (18.4%) [Gries et al. *J Heart Lung Transplant*. 2013; 32[5]: 525-532]. In another study by Dew et al, in 178 lung trans-



DR. AHYA

plant recipients, all PTSD occurred in the early months posttransplant with a median duration of symptoms of 12 months (IQR 7.2 to 18.5 months) [Dew et al. *Gen. Hosp Psychiatry*. 2012;34:127-138]. A higher burden of PTSD is noted in patients who are younger, have a lower income, have a previous history of a traumatic event, and have bronchiolitis obliterans (Gries et al. *J Heart Lung Transplant*. 2013;32[5]:525-532).

The challenges that remain include determining the true prevalence of PTSD in the lung transplant recipient in the LAS era using standard diagnostic criteria, documenting the adverse effects of PTSD on medical compliance, morbidity, and mortality; and developing interventions to mitigate the adverse effects of PTSD through well-designed multicenter prospective studies.

Vivek Ahya, MD
Steering Committee Member

Women's Health

Caregiver Burden in the ICU and Beyond

Family members of patients in the ICU who transition to the role of caregivers following discharge are at high risk for psychosocial distress. Post-intensive care syndrome-family (PICS-F) describes the symptoms of depression, posttraumatic stress, and anxiety commonly found in this population (Davidson et al. *Crit Care Med*. 2012;4(2):618-624). Women are more commonly called upon to adopt the role of caregiver for family members with chronic medical conditions or mental illnesses. Worldwide estimates indicate that 57% to 81% of all caregivers are women (Sharma et al. *World J Psych*. 2016;6[2]:7-17).

Family burden begins during the acute phase of critical illness. As surrogate decision-makers, they frequently face decisional conflict and decisional regret, especially in scenarios that limit life-sustaining therapies (Long et al. *Curr Opin Crit Care*.

2016;22:613-620). The prevalence of PICS-F is high as family members attempt to balance their role in the ICU with personal obligations (Choi et al. *J Korean Acad Nurs*. 2016;[46]2:159-167). Those who perceive that they are not receiving complete information from the medical team, and who do not find their physician comforting, have been shown to suffer a greater symptom burden (Davidson et al).

With the growing older adult population, and increased ICU survival, family members are often called upon to serve as caretakers to the chronically critically ill (Choi et al.). These caregivers have more depressive symptoms, worse health outcomes, and significant professional and personal lifestyle disruptions (Cameron, et al. *N Engl*



DR. PISANI



DR. BOURNIVAL

J Med. 2016;[374]19:1831-1841). In many caregivers, depressive symptoms persist at 1 year after ICU admission, with rates comparable to caretakers of patients with dementia (Haines et al. *Crit Care Med*. 2015;(43)5:1112-1120). Caregivers who are younger, female, minorities, and those with pre-existing depression are at especially high risk for worse mental health outcomes (Davidson et al; Cameron et al).

Caregivers of ICU survivors are vulnerable and undersupported. Interventions such as ICU diaries, telephone-based mindfulness exercises, and stress management strategies have shown promise in alleviating PICS-F symptoms (Choi et al.). During the acute ICU stay, how medical providers communicate, and how we help family members make sense of what has happened and their new roles as caregivers have an impact (Davidson et al.). From an individual in a study of psychosocial morbidity in caregivers of ICU survivors: "Leaving the hospital is not the end for some people. The next place is just as hard, sometimes worse" (Haines et al. Further studies are needed to identify interventions that will truly address this population's unique needs.

Margaret Pisani, MD, FCCP
Steering Committee Member
Nicole Bournival, MD
Fellow-in-Training Member



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¹ Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

² Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

³ Nykamp M., et al. "Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemodynamic instability." *J Vascular Surgery: Venous and Lymphatic Disorders* 2015; 3(5): 251-7.

⁴ Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

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