



CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



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In adults 65 and older, PCV13 was 75% effective for preventing vaccine-type strains of invasive pneumococcal disease.

PCV13 efficacy in elderly confirmed

BY MARY ANN MOON
Frontline Medical News

The 13-valent polysaccharide conjugate vaccine showed “significant efficacy” against vaccine-type strains of community-acquired pneumonia and vaccine-type invasive pneumococcal disease among elderly participants in a large clinical trial in the Netherlands.

The PCV13 vaccine’s efficacy in adults aged 65 years and older has never been determined until now.

It became possible to assess efficacy in this age group when a serotype-specific urinary antigen detection assay was developed.

The assay can identify *Streptococcus pneumoniae* polysaccharides in the urine of patients suspected of having pneumonia and avoids the need to isolate the organism in culture, Dr. Marc J.M. Bonten of Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (the Netherlands), and his associates wrote.

The researchers used the assay to assess PCV13 efficacy in 84,496 older adults who were randomly assigned to receive active vaccine (42,240 participants) or placebo (42,256) and followed for a mean of 4 years in the trial, which was sponsored by GlaxoSmithKline.

See **PCV13** • page 10

Reslizumab aces trials in asthma with eosinophilia

Exacerbations halved with reslizumab.

BY BRUCE JANCIN
Frontline Medical News

HOUSTON – Reslizumab, a next-generation molecular-based asthma therapy, achieved its primary and secondary endpoints and demonstrated favorable safety in patients with moderate to severe asthma and eosinophilia in two pivotal clinical trials.

“We believe that reslizumab is an effective therapy for controlling asthma in patients with elevated blood eosinophils who are inadequately controlled on medium- to high-dose inhaled corticosteroid-based regimens,” said Dr. Mario Castro, FCCP, who

presented the results of two phase III studies at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The frequency of clinical asthma exacerbations was reduced by more than half in reslizumab-treated patients, compared with controls in the two year-long studies. In addition, the reslizumab group experienced an early improvement in lung function as expressed in forced expiratory volume in 1 second (FEV₁) that was sustained throughout the year-long trials, as well as improvements in other measures of

See **Reslizumab** • page 7

Panel backs ICS/LABA for adults only

BY ELIZABETH MEHCATIE
Frontline Medical News

GAITHERSBURG, MD. – A Food and Drug Administration advisory panel supported approval of a fluticasone and vilanterol combination to treat asthma in adults – but the majority voted against approval for adolescents, citing a need for more safety and effectiveness data in that population.

GlaxoSmithKline has proposed that two fixed-dose combinations, 100 mcg or 200

mcg of the inhaled corticosteroid (ICS) fluticasone with 25 mcg of the long-acting beta-agonist (LABA) vilanterol in a dry powder inhaler, be approved for maintenance treatment of asthma in patients age 12 years and older, administered once per day.

The FDA approved the 100-mcg/25-mcg dose in 2013 to treat chronic obstructive pulmonary disease; GSK markets it as Breo Ellipta. To earn an asthma indication, the company submitted data from four studies,

See **ICS/LABA** • page 47

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October 24 - 28





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Reduce lung function decline

Delay IPF Progression with Esbriet



Indication

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

Select Important Safety Information

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

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

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

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

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



Introducing **Esbriet**[®]
(pirfenidone) capsules 267mg

Proven to delay progression in IPF²

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had $\geq 10\%$ decline in %FVC, $P < 0.001$). Treatment effect was evident at 13 weeks ($P < 0.001$) and increased through trial duration^{1,2,*†}
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)^{1,*‡}
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet¹
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide³

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and DL_{CO} between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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

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

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

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

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

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

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

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the $\geq 10\%$ decline category.

‡Stable was defined as no decline in lung function.

References: **1.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **2.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **3.** InterMune, Inc. Data on file.

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Esbriet[®]
(pirfenidone) capsules 267mg

Start here

Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

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

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*].

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*].

ADVERSE REACTIONS

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

- Liver Enzyme Elevations [see *Warnings and Precautions*]
- Photosensitivity Reaction or Rash [see *Warnings and Precautions*]
- Gastrointestinal Disorders [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 pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

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

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

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

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

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

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

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

Postmarketing Experience

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

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

DRUG INTERACTIONS**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 CYP1A Inhibitors

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

Moderate CYP1A 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.

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*].

USE IN SPECIFIC POPULATIONS**Pregnancy**

Teratogenic Effects: **Pregnancy Category C.**

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

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

Nursing Mothers

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

Pediatric Use

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

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.

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see *Dosage and Administration section 2.2 in full Prescribing Information*].

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

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.

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.

OVERDOSAGE

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

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

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*].

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*].

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*].

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.

Manufactured for:

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Brisbane, CA 94005 USA

INTERMUNE®

Respiratory harm declined with e-cigarette switch

BY BRUCE JANCIN

Frontline Medical News

HOUSTON – Asthmatic smokers who switched to electronic cigarettes showed evidence suggestive of respiratory harm reversal in a retrospective pilot study.

“Electronic cigarette use improves respiratory physiology and subjective asthma outcomes in asthmatic smokers,” Dr. Cristina Russo said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

She said that her small retrospective study is the first to examine the respiratory health impact of a switch to e-cigarettes by asthmatic smokers.

Each of the objective and subjective measures of asthma status evaluated in the study showed statistically

VITALS

Key clinical point: Asthmatic smokers who switched to electronic cigarettes showed significant 1-year improvements in lung function, methacholine-provoked airway hyperresponsiveness, and asthma-related quality of life.

Major finding: After use of e-cigarettes was initiated, self-reported daily consumption of conventional cigarettes fell from a mean of 21.9 per day at baseline to 5.0 at 6 months and 3.9 at 12 months of follow-up.

Data source: This retrospective pilot study included 18 asthmatic smokers.

Disclosures: The study was supported by a university grant and the Italian League Against Smoking. The presenter reported having no financial conflicts.

significant improvement 1 year after patients adopted e-cigarettes, and the e-cigarette users’ consumption of conventional cigarettes dropped precipitously, reported Dr. Russo of the University of Catania (Italy).

She and her colleagues in the university asthma clinic have taken to suggesting the use of e-cigarettes to their asthmatic smokers who haven’t

benefited from or aren’t interested in trying the more conventional approaches to smoking cessation or reduction, including medications. While abstinence from smoking is best, the available evidence indicates e-cigarettes are at least 95% less harmful than conventional cigarettes in the general population, she said.

The study included 18 smokers with mild to moderate asthma who began to use e-cigarettes and underwent spirometry and other testing at baseline and 6 and 12 months of follow-up.

Ten patients switched over to e-cigarettes exclusively; the other eight used conventional and e-cigarettes.

Among the study highlights: The mid-range forced expiratory flow (25%-75%) increased from 2.75 L/sec to 3.11 L/sec. And patients’ mean self-reported conventional cigarette consumption dropped from 21.9 per day at baseline to 5 at 6 months and 3.9 per day at 12 months.

Dr. Russo’s presentation sparked vigorous audience discussion. Several physicians cited a Centers for Disease Control and Prevention warning about the unknowns regarding e-cigarette safety, but others defended the “lesser of two evils” approach.

Dr. Russo called smoking and asthma “a dangerous liaison.” Smoking accelerates asthma patients’ decline in lung function, worsens persistent airways obstruction, and increases insensitivity to corticosteroids.

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CHEST Physician Is Online

CHEST Physician is available on the Web at chestphysician.org



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

Salutary changes following switch to e-cigarettes

	Baseline	12 months
Forced expiratory volume in 1 sec (FEV ₁)	3.3 L/sec	3.4 L/sec
Forced vital capacity	4.28 L	4.43 L
Midrange forced expiratory flow	2.75 L/sec	3.11 L/sec
Methacholine concentration required to produce a 20% fall in FEV ₁ from baseline	1.24 mg/mL	2.56 mg/mL
Asthma Control Questionnaire score	2.03	1.43
Mean conventional cigarettes per day	21.9	3.9

Note: Based on data from 18 smokers with mild to moderate asthma.

Source: Dr. Russo

CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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Exacerbations were halved

Reslizumab from page 1

asthma control, including quality of life, Dr. Castro, professor of pulmonary and critical care medicine and pediatrics at Washington University in St. Louis, said.

Elevated blood and sputum levels of eosinophils define an asthma phenotype at increased risk for serious asthma exacerbations. Reslizumab is a humanized monoclonal antibody that binds circulating interleukin-5 and prevents binding to the IL-5 receptor, thereby disrupting eosinophil production and function.

Dr. Castro presented two identically designed phase III, double-blind, placebo-controlled, 12-month studies totaling 953 adolescents and adults. They were randomized to intravenous reslizumab at 3 mg/kg or placebo every 4 weeks for a year.

The primary endpoint was frequency of clinical asthma exacerbations (CAEs), an independently adjudicated composite outcome that required an episode featuring an increase in corticosteroids, an asthma-related ER visit or unscheduled office visit, evidence of asthma worsening in the form of at least a 20% drop from baseline in

FEV₁ or a 30% reduction in peak expiratory flow rate on 2 consecutive days, and worsening clinical symptoms.

Participants averaged two CAEs during the year prior to enrollment.

The placebo-treated controls maintained that event rate during the two year-long studies, while the reslizumab-treated patients experienced 50% and 59% reductions relative to controls ($P < .0001$).

Reslizumab also increased the time to first CAE. In the two trials, 61% and 73% of reslizumab-treated

patients didn't develop a single CAE during 52 weeks, compared with 44% and 52% of controls.

The more CAEs a patient had in the year prior to enrollment, the greater the magnitude of benefit with reslizumab. While the relative risk reduction was 54%, compared

Continued on following page



SPIRIVA RESPIMAT has joined SPIRIVA HandiHaler to help patients with COPD breathe better

THAT'S THE MISSION OF THE MIST

For your newly diagnosed COPD patients, **SPIRIVA RESPIMAT** delivers a **slow-moving mist** that helps patients inhale the medication **independent of inspiratory effort**¹

As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).¹

The Mission continues at SPIRIVAmist.com

INDICATION

SPIRIVA HandiHaler and SPIRIVA RESPIMAT are indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for reducing COPD exacerbations.

IMPORTANT SAFETY INFORMATION for SPIRIVA HandiHaler and SPIRIVA RESPIMAT

SPIRIVA is contraindicated in patients with a history of hypersensitivity to tiotropium, ipratropium (atropine derivatives), or any component of either product.

SPIRIVA is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including urticaria, angioedema (swelling of lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA. Additionally, inhaled medicines, including SPIRIVA, may cause paradoxical bronchospasm. If any of these occurs, treatment with SPIRIVA should be stopped and other treatments considered.

Patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to SPIRIVA.

SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins.

SPIRIVA should be used with caution in patients with narrow-angle glaucoma or urinary retention. Prescribers should instruct patients to consult a physician immediately should any signs or symptoms of narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction occur.

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

Patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min for SPIRIVA HandiHaler and creatinine clearance of ≤ 60 mL/min for SPIRIVA RESPIMAT) and treated with SPIRIVA should be monitored closely for anticholinergic side effects.

SPIRIVA may interact additively with concomitantly used anticholinergic medications. Avoid coadministration with other anticholinergic-containing drugs.

The most common adverse reactions $>5\%$ incidence and exceeded placebo by $\geq 1\%$ with SPIRIVA HandiHaler (placebo) were upper respiratory tract infection 41% (37%), dry mouth 16% (3%), sinusitis 11% (9%), pharyngitis 9% (7%), non-specific chest pain 7% (5%), urinary tract infection 7% (5%), dyspepsia 6% (5%), and rhinitis 6% (5%). In addition, the most common reported adverse reaction $\geq 3\%$ incidence and higher than placebo from the 4-year trial with SPIRIVA HandiHaler (placebo) not included above were headache 5.7% (4.5%), depression 4.4% (3.3%), insomnia 4.4% (3.0%), and arthralgia 4.2% (3.1%).

The most common adverse reactions $>3\%$ incidence and higher than placebo with SPIRIVA RESPIMAT (placebo) were pharyngitis 11.5% (10.1%), cough 5.8% (5.5%), dry mouth 4.1% (1.6%), and sinusitis 3.1% (2.7%).

SPIRIVA capsules should not be swallowed and should only be inhaled through the mouth (oral inhalation) using the HandiHaler device and the HandiHaler device should not be used for administering other medications.

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

Please see Brief Summary for SPIRIVA RESPIMAT and SPIRIVA HandiHaler on adjoining pages.

Reference: 1. SPIRIVA RESPIMAT [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP,

comments: Asthma is a highly prevalent disease in urban America and one that remains challenging to treat. The patients attending my downtown clinic have persistent asthma complicated by obesity, pregnancy, and active smoking. Their condition is exacerbated because of substandard insurance, substandard housing, and inadequate medical follow-up. The monoclonal IL-5 antibody reslizumab offers promise, but the glowing reports raise questions for me. I know that at least two other companies are developing anti-IL-5 monoclonals. Will they be different from reslizumab? Will an urban population benefit to the same degree as the population in these reports? Will my patients have access to these drugs, or will we be mired in a world of unaffordable co-pays and declined pre-authorizations?



ONCE DAILY
SPIRIVA[®] RESPIMAT[®]
(tiotropium bromide)
INHALATION SPRAY

Boehringer
Ingelheim

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Once-Daily
SPIRIVA[®] HandiHaler[®]
(tiotropium bromide inhalation powder)

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PC-SV-0011-PROF

Continued from previous page

with placebo, it climbed to 64% in patients with four or more CAEs in the previous year.

FEV₁ improved after the first dose of reslizumab. Placebo-subtracted gains of 0.126 L in one trial and 0.09 L in the other were sustained

throughout the 52 weeks.

The reslizumab group also outperformed controls in terms of Asthma Control Questionnaire scores and Asthma Quality of Life Questionnaire scores. For example, 74% and 73% of reslizumab-treated patients in the two studies experienced at least a 0.5-point improvement in the AQLQ,

which is considered the minimal clinically important difference, compared with 65% and 62% of controls.

Study discontinuation due to adverse events occurred in 2% of patients on reslizumab, with worsening asthma the No. 1 reason.

Two patients on reslizumab had anaphylactoid reactions; neither re-

quired epinephrine. Three percent of reslizumab-treated patients developed low-titer, generally transient antidrug antibodies that didn't affect eosinophil levels, which dropped with the first dose of reslizumab and stayed low throughout the studies.

Reslizumab is one of a cluster of novel agents in development for se-

SPIRIVA® Respimat® (tiotropium bromide) Inhalation Spray

FOR ORAL INHALATION

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

INDICATIONS AND USAGE: SPIRIVA RESPIMAT (tiotropium bromide) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA RESPIMAT is indicated to reduce exacerbations in COPD patients.

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

WARNINGS AND PRECAUTIONS: Not for Acute Use: SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for COPD and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

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

ADVERSE REACTIONS: The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see Warnings and Precautions]; Paradoxical bronchospasm [see Warnings and Precautions]; Worsening of narrow-angle glaucoma [see Warnings and Precautions]; Worsening of urinary retention [see Warnings and Precautions]. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. The SPIRIVA RESPIMAT clinical development program included ten placebo controlled clinical trials in COPD. Two trials were four-week cross-over trials and eight were parallel group trials. The parallel groups trials included a three week dose-ranging

trial, two 12-week trials, three 48-week trials, and two trials of 4-week and 24-week duration conducted for a different program that contained tiotropium bromide 5 mcg treatment arms. The primary safety database consists of pooled data from the 7 randomized, parallel-group, double-blind, placebo-controlled studies of 4-48 weeks in treatment duration: These trials included 6565 adult COPD patients (75% males and 25% females) 40 years of age and older. Of these patients, 3282 patients were treated with SPIRIVA RESPIMAT and 3283 received placebo. The SPIRIVA RESPIMAT group was composed mostly of Caucasians (78%) with a mean age of 65 years and a mean baseline percent predicted post-bronchodilator FEV₁ of 46%. In these 7 clinical trials, 68.3% of patients exposed to SPIRIVA RESPIMAT reported an adverse event compared to 68.7% of patients in the placebo group. There were 68 deaths in the SPIRIVA RESPIMAT treatment group (2.1%) and 52 deaths (1.6%) in patients who received placebo. The percentage of SPIRIVA RESPIMAT patients who discontinued due to an adverse event were 7.3% compared to 10% with placebo patients. The percentage of SPIRIVA RESPIMAT patients who experienced a serious adverse event were 15.0% compared to 15.1% with placebo patients. In both groups, the adverse event most commonly leading to discontinuation was COPD exacerbation (SPIRIVA RESPIMAT 2.0%, placebo 4.0%) which was also the most frequent serious adverse event. The most commonly reported adverse reactions were pharyngitis, cough, dry mouth, and sinusitis (Table 1). Other adverse reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, dysuria, and urinary retention. Table 1 shows all adverse reactions that occurred with an incidence of >3% in the SPIRIVA RESPIMAT treatment group, and a higher incidence rate on SPIRIVA RESPIMAT than on placebo.

Table 1 Number (percentage) of COPD patients exposed to SPIRIVA RESPIMAT with adverse reactions >3% (and higher than placebo): Pooled data from 7 clinical trials with treatment periods ranging between 4 and 48 weeks in COPD patients

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

*Adverse reactions include a grouping of similar terms. Other reactions that occurred in the SPIRIVA RESPIMAT group at an incidence of 1% to 3%, and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo included: *Cardiac disorders:* palpitations; *Gastrointestinal disorders:* constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders:* dizziness; *Respiratory system disorders (Upper):* dysphonia; *Skin and subcutaneous tissue disorders:* pruritus, rash; *Renal and urinary disorders:* urinary tract infection. **Less Common Adverse Reactions:** Among the adverse reactions observed in the clinical trials with an incidence of <1% and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo were: dysphagia, gingivitis, intestinal obstruction including ileus paralytic, joint swelling, dysuria, urinary retention, epistaxis, laryngitis, angioedema, dry skin, skin infection, and skin ulcer. **Postmarketing Experience:** In addition to the adverse reactions observed during the SPIRIVA RESPIMAT clinical trials, the following adverse reactions have been identified during the worldwide use of SPIRIVA RESPIMAT and another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder): glaucoma, intraocular pressure increased, vision blurred, atrial fibrillation, tachycardia, supraventricular tachycardia, bronchospasm, glossitis, stomatitis, dehydration, insomnia, hypersensitivity (including immediate reactions), and urticaria.

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

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at approximately 660 and 6 times the recommended human daily inhalation dose (RHDID), respectively (on a mg/m² basis at maternal inhalation doses of 1.471 and 0.007 mg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 45 times the RHDID (on a mg/m² basis at a maternal inhalation dose of 0.078 mg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDID (on a mg/m² basis at a maternal inhalation dose of 0.4 mg/kg/day). Such effects were not observed at approximately 4 and 80 times the RHDID, respectively (on a mg/m² basis at inhalation doses of 0.009 and 0.088 mg/kg/day in rats and rabbits, respectively). **Labor and Delivery:** The safety and effectiveness of SPIRIVA RESPIMAT has not been studied during labor and delivery. **Nursing Mothers:** Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA RESPIMAT is administered to a nursing woman. **Pediatric Use:** SPIRIVA RESPIMAT is not indicated for use in children. The safety and effectiveness of SPIRIVA RESPIMAT in pediatric patients have not been established. **Geriatric Use:** Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted. Thirty nine percent of SPIRIVA RESPIMAT clinical trial patients were between 65 and 75 years of age and 14% were greater than or equal to 75 years of age. The adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Renal Impairment:** Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [see Warnings and Precautions]. **Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

OVERDOSAGE: High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. Treatment of overdose consists of discontinuation of Spiriva Respimat together with institution of appropriate symptomatic and/or supportive therapy.

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SVR-BS-10/14 304478-01 SVR636408PROF

vere or treatment-resistant asthma. These are targeted therapies directed at specific patient phenotypes. Biomarkers such as eosinophilia provide guidance as to the specific asthmatic inflammatory pathways involved.

In an interview, Dr. James E. Gern, who wasn't involved in the reslizum-

ab studies, said the various severe asthma phenotypes account for a relatively small proportion of the total asthma population, but a tremendously disproportionate amount of health care utilization.

These new medications will "be indicated for a relatively small number of people. But for those people, it'll

make a huge difference because of the huge burden that severe asthma has on quality of life," said Dr. Gern, professor of pediatrics at the University of Wisconsin, Madison.

The two reslizumab studies were sponsored by Teva. Dr. Castro is on the company's speakers' bureau and receives grants from more than

a dozen companies as well as from the National Institutes of Health and Centers for Disease Control and Prevention.

The study results are published online (Lancet Respir. Med. 2015 [doi.org/10.1016/S2213-2600(15)00042-9]).

bjancin@frontlinemedcom.com

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)

Capsules for Respiratory Inhalation

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

DO NOT Swallow SPIRIVA Capsules

FOR ORAL INHALATION ONLY with the HandiHaler Device

INDICATIONS AND USAGE: SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HandiHaler is indicated to reduce exacerbations in COPD patients.

CONTRAINDICATIONS: SPIRIVA HandiHaler is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any components of SPIRIVA capsules [see **WARNINGS AND PRECAUTIONS**]. In clinical trials and postmarketing experience with SPIRIVA HandiHaler, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

WARNINGS AND PRECAUTIONS: Not for Acute Use: SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy). **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching, may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA HandiHaler. In addition, SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins. **Paradoxical Bronchospasm:** Inhaled medicines, including SPIRIVA HandiHaler, can produce paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered. **Worsening of Narrow-Angle Glaucoma:** SPIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** SPIRIVA HandiHaler should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects.

ADVERSE REACTIONS: The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see **Warnings and Precautions**]; Paradoxical bronchospasm [see **Warnings and Precautions**]; Worsening of narrow-angle glaucoma [see **Warnings and Precautions**]; Worsening of urinary retention [see **Warnings and Precautions**]. **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. **6-Month to 1-Year Trials:** The data described below reflect exposure to SPIRIVA HandiHaler in 2663 patients. SPIRIVA HandiHaler was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV₁) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected. The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention. Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Rx only

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA HandiHaler treatment group, but were $< 1\%$ in excess of the placebo group. Other reactions that occurred in the SPIRIVA HandiHaler group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *Gastrointestinal System Disorders:* gastro-intestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Infections:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis; *Vision Disorder:* cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of $< 1\%$ were atrial fibrillation, supra-ventricular tachycardia, angioedema, and urinary retention. In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [see *Use in Specific Populations*]. Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials. **4-Year Trial:** The data described below reflect exposure to SPIRIVA HandiHaler in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$, adverse reactions included (SPIRIVA HandiHaler, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%). **Additional Adverse Reactions:** Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HandiHaler than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling. **Postmarketing Experience:** Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler. 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 adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

DRUG INTERACTIONS: Sympathomimetics, Methylxanthines, Steroids: SPIRIVA HandiHaler has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse drug reactions. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HandiHaler with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see **Warnings and Precautions and Adverse Reactions**]. **Cimetidine, Ranitidine:** No clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects, Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to approximately 660 and 6 times the recommended human daily inhalation dose (RHDD) on a mg/m² basis, respectively. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 35 times the RHDD on a mg/m² basis. In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDD on a mg/m² basis. Such effects were not observed at inhalation doses of approximately 4 and 80 times the RHDD on a mg/m² basis in rats and rabbits, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies. **Labor and Delivery:** The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery. **Nursing Mothers:** Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman. **Pediatric Use:** SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established. **Geriatric Use:** Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were < 65 years, 375 were 65 to 74 years, and 105 were ≥ 75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted. **Renal Impairment:** Patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [see **Warnings and Precautions**]. **Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

OVERDOSAGE: High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium. **Accidental Ingestion: Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.** A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day. No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7300, 120,000, and 850 times the recommended human daily inhalation dose on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

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Self-reported penicillin allergy may be chronic urticaria

BY DEEPAK CHITNIS

Frontline Medical News

HOUSTON – Patients with self-reported penicillin allergy may actually have chronic urticaria, Dr. Susanna G. Silverman, of the University of Pennsylvania, Philadelphia reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

A retrospective chart review of 1,419 patients with self-reported penicillin allergy revealed that 12% had a diagnosis of chronic urticaria, a significantly higher percentage than the typical prevalence range of 0.5%-5% for chronic urticaria in the general population. Of the 175 patients who had chronic urticaria, 84% were female, and 53% were white.

The study included patients at the University of Pennsylvania's allergy and immunology clinic who self-reported penicillin allergy from June 2007 to August 2014.

Patients were identified as having penicillin allergy if penicillin, amoxicillin, amoxicillin-clavulanate, or piperacillin-tazobactam were present on the allergy list of their medical records.

Dr. Silverman then identified all patients from that group who also received a diagnosis of urticaria – a total of 343 patients – then narrowed the list to those who were diagnosed with chronic urticaria or the presence of urticaria for at least 6 weeks.

"We think it's important for physicians to think about this and to ask patients about symptoms of chronic urticaria when they report penicillin allergy," Dr. Silverman noted, "to better determine what is truly penicillin allergy versus simply chronic urticaria symptoms."

Dr. Silverman did not report any financial disclosures.

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Two new strains advised for 2015-2016 flu vaccine

BY ELIZABETH MEHCATIE
Frontline Medical News

SILVER SPRING, MD. – Two components of the trivalent and quadrivalent influenza vaccines used during the current season should be replaced for the 2015-2016 vaccine, including the influenza A(H3N2) component, a Food and Drug Administration advisory panel has stated.

During the current season, most of the influenza activity in the United States has been due to influenza A (H3N2), and more than two-thirds of the A (H3N2) viruses tested at the Centers for Disease Control and Prevention have “drifted” from the A (H3N2) strain included in the current vaccines, reducing their effectiveness.

The FDA’s Vaccines and Related Biologicals Products Advisory Committee voted at a meeting March 4 to recommend that the following viruses be used for the 2015-2016 trivalent vaccine: an A/California/7/2009 (H1N1)pdm09-like virus; an A/Switzerland/9715293/2013 (H3N2)-like virus; and a B/Phuket/3073/2013-like virus (B/Yamagata lineage).

The A (H3N2) strain and the B/Yamagata lineage strain would replace the strains in the current vaccine.

The committee recommended a B/Brisbane/60/2008-like virus (B/Victoria lineage) for the second influenza B strain in the quadrivalent vaccine, which is included in the current quadrivalent vaccine.

The panel votes separately on the strains; all votes were unanimous, except for the vote on the



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B/Yamagata lineage strain in the trivalent vaccine, which was supported by a 14-1 vote.

The FDA panel’s recommendation is the same as the recommendation made recently by the World Health Organization for next season’s influenza vaccines in the Northern Hemisphere.

Every year, the FDA panel meets at this time and considers the WHO recommendation, as well as information that includes influenza surveillance and epidemiology data in North America and worldwide.

Hospitalization rates for laboratory-confirmed

influenza this season have been markedly higher among people aged 65 years and older, compared with younger age groups.

In late February, the preliminary estimate of hospitalizations in this age group was 51.7 cases per 100,000 people, compared with about 27 per 100,000 during the last season.

This is the highest rate recorded for this age group since surveillance began during the 2005-2006 season, according to Dr. Lisa Grohskopf of the epidemiology & prevention branch in the CDC’s influenza division.

When asked why the hospitalization rate has been so high among the elderly, Dr. Grohskopf said that A (H3N2)-predominant seasons tend to be associated with more severe disease, and vaccine efficacy this season was reduced.

Updated estimates of the current vaccine effectiveness against influenza A (H3N2) viruses, provided by the CDC is 18%. For all influenza viruses overall, estimated effectiveness is 19%, indicating that the flu vaccine reduced a person’s risk of having to seek medical care at a doctor’s office for flu illness by 19%, according to the update.

During seasons when the vaccine is a good match for circulating viruses, vaccine effectiveness is in the 60% range, according to speakers at the FDA panel meeting.

The FDA usually follows the recommendations of its panel members. None of the panelists had disclosures.

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Vaccine efficacy confirmed

PCV13 from page 1

sored by Pfizer Inc.

In the per-protocol analysis, vaccine efficacy was 46% for preventing a first episode of vaccine-type community-acquired pneumonia, 45% for preventing nonbacteremic and noninvasive vaccine-type community-acquired pneumonia, and 75% for preventing vaccine-type invasive pneumococcal disease.

Evidence of the vaccine’s efficacy became apparent shortly after vaccination occurred and persisted throughout the duration of the study.

There was no evidence of any safety concerns in the patients who received the active vaccine, wrote Dr. Bonten and his associates (N. Engl. J. Med. 2015 March 19 [doi:10.1056/NEJMoa1408544]).

The PCV13 vaccine did not show efficacy in preventing death from any cause, but the number of deaths associated with pneumococcal disease in this study was too small to allow a meaningful analysis of this outcome, Dr. Bonten and his associates noted.

VITALS

Key clinical point: The 13-valent pneumococcal polysaccharide conjugate vaccine is effective against community-acquired pneumococcal pneumonia in adults aged 65 years and older.

Major finding: Vaccine efficacy was 46% for preventing a first episode of vaccine-type strains of community-acquired pneumonia, 45% for preventing nonbacteremic and noninvasive vaccine-type strains of community-acquired pneumonia, and 75% for preventing vaccine-type strains of invasive pneumococcal disease.

Data source: An industry-sponsored randomized placebo-controlled double-blind trial involving 84,496 Dutch adults aged 65 years and older followed for a mean of 4 years after vaccination.

Disclosures: Pfizer sponsored the study. Dr. Bonten and several associates reported ties to Pfizer, and his associates also reported ties to GlaxoSmithKline, Roche, and Novartis.

FDA’s app provides real-time drug shortage information

BY ELIZABETH MEHCATIE
Frontline Medical News

A mobile app that provides up-to-date information on drug shortages has been launched by the Food and Drug Administration.

The mobile application is “specifically designed to speed public access to valuable information about drug shortages,” namely, current and resolved drug shortages and discontinuations of drug shortages, according to the FDA statement.

One can search by a drug’s generic name, active ingredient, or therapeutic category, and can use the app to report a drug shortage or a supply issue to the FDA.

The app provides “easier and faster access to important drug shortage information,” Capt. Valerie Jensen, R.Ph., associate director of the drug shortages program in the FDA’s Center for Drug Evaluation and Research, said in the statement. “Health care profession-



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als and pharmacists need real-time information about drug shortages to make treatment decisions.”

The app is free and can be downloaded via iTunes for Apple devices and the Google Play store for Android devices, searching for “FDA Drug Shortages.”

More information is available on the FDA’s web site at <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

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PULMONARY PERSPECTIVES: ECMO – The new state of the art?

BY DR. PAUL C. SAUNDERS

The treatment of severe cardiac and respiratory failure has historically carried a high mortality – up to 50% in some series. Since the 1970s, extracorporeal membrane oxygenation (ECMO) has been used to treat patients with refractory shock, but until recently excessive morbidity and technical challenges left ECMO as a therapy offered to a limited group of patients at select centers. Over the past few years, a unique confluence of events, including the H1N1 pandemic, sparked the resurgence of ECMO in ICUs around the world. Since this time, interest in the use of ECMO in a variety of clinical settings has continued to grow (MacLaren et al. *Intensive Care Med.* 2012;38[2]:210). More centers are now using ECMO to support patients with a growing set of indications, and more reports about ECMO are added to the literature each year. Despite its rapid growth, uncertainty persists regarding the ultimate role of ECMO in the treatment of severe cardiopulmonary failure, given the limited data available (Leligdowicz et al. *Curr Opin Crit Care.* 2015;21[1]:13).

ECMO supports the patient by circulating venous blood through an extracorporeal circuit consisting of a blood pump and an oxygenator, which adds oxygen and removes carbon dioxide. The oxygenated blood is then returned back to the venous circulation (venovenous ECMO) or the arterial circulation (venoarterial ECMO). Venovenous ECMO is used to provide respiratory support, whereas venoarterial ECMO, as it is providing pressurized blood flow to the systemic circulation, can provide full cardiopulmonary support. Cannula locations are dependent on the type of support needed. Venovenous ECMO is frequently accomplished by draining blood from the inferior vena cava via the femoral vein and returning oxygenated blood to the right atrium via the internal jugular vein. A newer, dual-lumen cannula can drain blood from the inferior vena cava and return it to the right atrium as well, eliminating the need for lower body cannulation and allowing for better patient mobilization. One of the most important aspects of venovenous ECMO is lung rest, as it facilitates aggressive lung protective strategies that can allow lung injury to heal while minimizing barotrauma (Brodie et al. *N Engl J Med.* 2011;365[20]:1905).

Venoarterial ECMO is most com-

monly achieved with femoral venous drainage and femoral arterial return, as these cannulae can be deployed rapidly in any location. Alternatively, oxygenated blood can be returned to the axillary artery, which has the advantage of antegrade flow, which can be beneficial in providing the most physiologic means of support. Venoarterial ECMO is powerful in cases of profound cardiogenic shock, as flow rates well over 5 L can be achieved. Venoarterial ECMO can also be a useful tool as a “bridge to decision” device to stabilize patients until they can safely undergo more definitive left ventricular assist device (LVAD) implantation (Takayama et al. *J Heart Lung Transplant.* 2013;32[1]:106).

The earliest ECMO circuits were essentially repurposed heart-lung machines. When used to support patients for periods longer than a cardiac bypass run, they had shortcomings. They were labor-intensive to set up

A newer, dual-lumen cannula can drain blood from the inferior vena cava and return it to the right atrium as well, eliminating the need for lower body cannulation and allowing for better patient mobilization.

and manage in the ICUs, and therefore, required a perfusionist at the bedside. The oxygenators used had a relatively short lifespan and were subject to clotting, air embolization, and unpredictable failure. Similarly, roller pumps produced excessive damage to blood elements, were challenging to maintain, and were laborious to set up and prime (Leligdowicz et al. *Curr Opin Crit Care.* 2015;21[1]:13). Morbidity was high and complications, including bleeding, stroke, and infections, were common.

Published reports from the early ECMO experience were troubling and did little to encourage wider adoption of ECMO in cardiopulmonary failure. In a controlled, multicenter trial of ECMO for acute respiratory distress syndrome (ARDS) published in *JAMA* in 1979, 90 patients were randomized to ECMO vs conventional therapy. ECMO did not improve survival; in fact, both groups had excessive mortality (>80%) (Zapol et al. *JAMA.* 1979;242[20]:2193). However, these results probably reflect the state of

ARDS treatment and the primitive ECMO circuits of the era rather than the efficacy of ECMO support (Del Sorbo et al. *Lancet Respir Med.* 2014;2[2]:154).

In the face of negative reports, the use of ECMO was stagnant for roughly 30 years, until key events in the late 2000s caused a paradigm shift. Cardiopulmonary bypass technology had advanced significantly, with a new class of smaller, more efficient centrifugal pumps that are not only more resistant to clotting but also produce less hemolysis by limiting blood contact with foreign surfaces. Their operation was more intuitive, set-up time was shorter, and they required less priming volume.

Similar advancements had been made in oxygenators, with the rise of polymethylpentene hollow-fiber oxygenators that boasted a lifespan measured in weeks, not days. More resistant to thrombosis and foaming, they were safer to maintain over extended periods and also produced less inflammatory response (Leligdowicz et al. *Curr Opin Crit Care.* 2015; 21[1]:13). Due to these advances, smaller, percutaneous ventricular assist devices were introduced for acute circulatory support, promising faster, easier implementation of support for critically ill patients. In addition, complications were minimized, with improvements in bleeding and neurologic adverse events.

These advances were reflected in the next multicenter trial of ECMO for ARDS, the CESAR trial, published in *Lancet* in 2009. Performed in the United Kingdom, 180 patients with ARDS were randomized to conventional therapy vs ECMO support. While serious concerns have been raised about the study’s methodology, use of ECMO was found to significantly improve survival (Peek et al. *Lancet.* 2009;374[9698]:1351).

In April 2009, cases of influenza A (H1N1) were initially reported in Mexico, and, over the next few months, had spread rapidly across the globe. By 2010, the Centers for Disease Control and Prevention had estimated approximately 60 million cases of influenza A (H1N1) in the United States, leading to over 270,000 hospitalizations and over 12,000 deaths.

Especially frightening to those working in ICUs, 87% of H1N1 deaths occurred in patients under 65 years of age. Working adults had an 8- to 12-times greater risk of hospitalization and death compared with seasonal influenza over the past 25 years (Shrestha et al. *Clin Infect*

Dis. 2011;52(suppl 1):S75). Many of these younger patients presented with rapidly progressive ARDS, and many were treated aggressively using ECMO support, with favorable outcomes, as first reported in Australia and New Zealand (ANZ ECMO Influenza Investigators. *JAMA.* 2009;302[17]:1888). As a result, worldwide use of ECMO spiked in response to the influenza A (H1N1) pandemic. Over time, centers gained experience using these safer, more

Worldwide use of ECMO spiked in response to the influenza A (H1N1) pandemic. Over time, centers gained experience using these safer, more rapidly deployable, and more easily transportable ECMO circuits.

rapidly deployable, and more easily transportable ECMO circuits (Combes et al. *Am J Respir Crit Care Med.* 2014;190[5]:488).

Since 2009, the use of ECMO has continued to grow. Data from the Extracorporeal Life Support Organization (ELSO) show over 250 ECMO centers worldwide, with over 5,000 total ECMO cases per year.

PubMed citations also show a dramatic increase in scholarly reports related to ECMO from the late 2000s, continuing to rise into 2015.

The increased use of the technology has also expanded the indications for ECMO support. Venovenous ECMO is most commonly used to support patients with respiratory failure due to ARDS but can also support patients waiting for lung transplantation, suffering posttransplant graft dysfunction, or even patients with postpneumonectomy ARDS.

The Extracorporeal Life Support Organization (ELSO) guidelines outline triggers for venovenous ECMO, including: hypoxic respiratory failure when risk of mortality is >80%, carbon dioxide retention (CO₂) on mechanical ventilation despite high plateau pressures, and severe air leak syndromes (*ELSO Guidelines*, December 2013. www.elseo.org).

Venoarterial ECMO is used in cardiogenic shock from acute coronary syndromes, acute decompensated heart failure, myocarditis, pulmonary embolism, postcardiotomy shock, and primary graft failure after cardiac transplantation. Some centers

Continued on page 14

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INDICATION

VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates). VIBATIV should be reserved for use when alternative treatments are not suitable.

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)
- *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or
- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV may be initiated as empiric therapy before results of these tests are known. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.



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IMPORTANT SAFETY INFORMATION

Mortality

Patients with pre-existing moderate/severe renal impairment (CrCl \leq 50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl \leq 50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity

New onset or worsening renal impairment occurred in patients who received VIBATIV. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function.

Monitor renal function in all patients receiving VIBATIV prior to initiation of treatment, during treatment, and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.

Fetal Risk

Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

Contraindication

VIBATIV is contraindicated in patients with a known hypersensitivity to the drug.

Hypersensitivity Reactions

Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin.

Geriatric Use

Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

Infusion Related Reactions

VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red-man Syndrome"-like reactions including: flushing of the upper body, urticaria, pruritus, or rash.

QTc Prolongation

Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, VIBATIV prolonged the QTc interval. Use of VIBATIV should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

Most Common Adverse Reactions

The most common adverse reactions (greater than or equal to 10% of patients treated with VIBATIV) were taste disturbance, nausea, vomiting, and foamy urine.

Continued from page 11

have been aggressively using ECMO support in patients suffering cardiac arrest from myriad causes, with so-called "E-CPR" (Lawler et al. *Circulation*. 2015;131[7]:676).

The rapid deployment possible with the latest generation of ECMO

technology has given rise to specialized ECMO teams within hospitals, similar to traditional code teams, which can be quickly summoned to evaluate and offer mechanical support if indicated. Given the rapid priming and percutaneous deployment of the modern ECMO circuit, patients are more frequently placed

on ECMO outside of the operating room, where cannulation was traditionally performed. Patients can be easily and safely placed on ECMO in varied locations throughout the hospital, including the ED, ICU, and the cardiac catheterization laboratory. The growth of ECMO teams has facilitated closer working relationships

between critical care specialists, pulmonologists, surgeons, and cardiologists, as well as other staff members (nurses, respiratory therapists, etc) critical to a successful program.

The greater accessibility of ECMO has led to more hospitals seeking to offer the therapy to their critically ill patients. What was once limited to a select group of tertiary medical centers is now offered at a wider range of facilities (Combes et al. *Am J Respir Crit Care Med*. 2014;190[5]:488).

Despite the many improvements in the technical aspects of ECMO support, the available data are still limited. While the older randomized clinical trials failed to show any benefit from ECMO support, the CESAR

Venovenous ECMO is most commonly used to support patients with ARDS but can also support patients waiting for lung transplantation, suffering posttransplant graft dysfunction, or even patients with postpneumectomy ARDS.

trial, while its methodology has been questioned, did demonstrate a survival benefit in patients with ARDS. However, the remaining data to support the use of ECMO comes from cohort studies and case series. The ongoing EOLIA trial (Extracorporeal Membrane Oxygenation to Rescue Lung Injury in Severe Acute Respiratory Distress Syndrome, NCT01470703) will serve as an international, randomized, multicenter investigation of venovenous ECMO for the treatment of ARDS. Until the data are available, the expansion of ECMO must be tempered with caution as evidence is still lacking on which patients truly benefit from ECMO (Tramm et al. *Cochrane Database Syst Rev*. 2015;1:CD010381).

Technologic advances have made ECMO therapy widely adaptable to many clinical situations and easily available at more medical centers. In contrast to the circuits of the past, current ECMO support is easier to implement and safer to operate.

As more data are collected, a more critical evaluation of the role of ECMO in the treatment of cardiopulmonary failure will finally be possible. Until then, enthusiasm should be tempered with caution as we move forward into this new era of mechanical support.

Dr. Saunders is with the Division of Cardiothoracic Surgery, Maimonides Medical Center, Brooklyn, New York.

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VIBATIV® (telavancin) for injection, for intravenous use

Rx ONLY

BRIEF SUMMARY. See package insert available at www.vibativ.com for full Prescribing Information, including Boxed Warning and Medication Guide.

INDICATIONS AND USAGE: VIBATIV is a lipoglycopeptide antibacterial drug indicated for the treatment of the following infections in adult patients caused by designated susceptible bacteria:

- Complicated skin and skin structure infections (cSSSI)
- Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*. VIBATIV should be reserved for use when alternative treatments are not suitable.

CONTRAINDICATIONS: VIBATIV is contraindicated in patients with known hypersensitivity to telavancin.

WARNINGS: Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients.

Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. Adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans.

WARNINGS AND PRECAUTIONS: Increased Mortality in Patients with HABP/VABP and Pre-existing Moderate to Severe Renal Impairment (CrCl ≤50 mL/min): In the analysis of patients (classified by the treatment received) in the two combined HABP/VABP trials with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min), all-cause mortality within 28 days of starting treatment was 95/241 (39%) in the VIBATIV group, compared with 72/243 (30%) in the vancomycin group. All-cause mortality at 28 days in patients without pre-existing moderate/severe renal impairment (CrCl >50 mL/min) was 86/510 (17%) in the VIBATIV group and 92/510 (18%) in the vancomycin group. Therefore, VIBATIV use in patients with baseline CrCl ≤50 mL/min should be considered only when the anticipated benefit to the patient outweighs the potential risk. **Decreased Clinical Response in Patients with cSSSI and Pre-existing Moderate/Severe Renal Impairment (CrCl ≤50 mL/min):** In a subgroup analysis of the combined cSSSI trials, clinical cure rates in the VIBATIV-treated patients were lower in patients with baseline CrCl ≤50 mL/min compared with those with CrCl >50 mL/min. A decrease of this magnitude was not observed in vancomycin-treated patients. Consider these data when selecting antibacterial therapy for use in patients with cSSSI and with baseline moderate/severe renal impairment. **Nephrotoxicity:** In both the HABP/VABP trials and the cSSSI trials, renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). The renal adverse event rates were also higher in patients who received concomitant medications known to affect kidney function (e.g., non-steroidal anti-inflammatory drugs, ACE inhibitors, and loop diuretics). Monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving VIBATIV. Values should be obtained prior to initiation of treatment, during treatment (at 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed. In patients with renal dysfunction, accumulation of the solubilizer hydroxypropyl-beta-cyclodextrin can occur. **Pregnant Women and Women of Childbearing Potential:** Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. VIBATIV caused adverse developmental outcomes in 3 animal species at clinically relevant doses. This raises concern about potential adverse developmental outcomes in humans. Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment. **Hypersensitivity Reactions:** Serious and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. Discontinue VIBATIV at first sign of skin rash, or any other sign of hypersensitivity. Telavancin is a semi-synthetic derivative of vancomycin; it is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-reactivity to telavancin. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin. **Infusion-Related Reactions:** VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause "Red-man Syndrome"-like reactions including: flushing of the upper body, urticaria, pruritus, or rash. Stopping or slowing the infusion may result in cessation of these reactions. **Clostridium difficile-Associated Diarrhea:** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should

be instituted as clinically indicated. **Development of Drug-Resistant Bacteria:** Prescribing VIBATIV in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. As with other antibacterial drugs, use of VIBATIV may result in overgrowth of nonsusceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken. **QTc Prolongation:** In a study involving healthy volunteers, doses of 7.5 and 15 mg/kg of VIBATIV prolonged the QTc interval. Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. Patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy were not included in clinical trials of VIBATIV. Use of VIBATIV should be avoided in patients with these conditions. **Coagulation Test Interference:** Although telavancin does not interfere with coagulation, it interfered with certain tests used to monitor coagulation, when conducted using samples drawn 0 to 18 hours after VIBATIV administration for patients being treated once every 24 hours. Blood samples for these coagulation tests should be collected as close as possible prior to a patient's next dose of VIBATIV. Blood samples for coagulation tests unaffected by VIBATIV may be collected at any time. No evidence of increased bleeding risk has been observed in clinical trials with VIBATIV. Telavancin has no effect on platelet aggregation. Furthermore, no evidence of hypercoagulability has been seen, as healthy subjects receiving VIBATIV have normal levels of D-dimer and fibrin degradation products.

ADVERSE REACTIONS: In the cSSSI clinical trials, serious adverse events were reported in 7% (69/929) of patients treated with VIBATIV and most commonly included renal, respiratory, or cardiac events. Serious adverse events were reported in 5% (43/938) of vancomycin-treated patients, and most commonly included cardiac, respiratory, or infectious events. Treatment discontinuations due to adverse events occurred in 8% (72/929) of patients treated with VIBATIV, the most common events being nausea and rash (~1% each). Treatment discontinuations due to adverse events occurred in 6% (53/938) of vancomycin-treated patients, the most common events being rash and pruritus (~1% each). The most common adverse events occurring in ≥10% of VIBATIV-treated patients were taste disturbance, nausea, vomiting, and foamy urine. The following table displays the incidence of treatment-emergent adverse drug reactions reported in ≥2% of patients treated with VIBATIV possibly related to the drug.

	VIBATIV (N=929)	Vancomycin (N=938)
Body as a Whole		
Rigors	4%	2%
Digestive System		
Nausea	27%	15%
Vomiting	14%	7%
Diarrhea	7%	8%
Metabolic and Nutritional		
Decreased appetite	3%	2%
Nervous System		
Taste disturbance*	33%	7%
Renal System		
Foamy urine	13%	3%

*Described as a metallic or soapy taste.

In HABP/VABP clinical trials, serious adverse events were reported in 31% of patients treated with VIBATIV and 26% of patients who received vancomycin. Treatment discontinuations due to adverse events occurred in 8% (60/751) of patients who received VIBATIV, the most common events being acute renal failure and electrocardiogram QTc interval prolonged (~1% each). Treatment discontinuations due to adverse events occurred in 5% (40/752) of vancomycin-treated patients, the most common events being septic shock and multi-organ failure (<1%). The following table displays the incidence of treatment-emergent adverse drug reactions reported in ≥5% of HABP/VABP patients treated with VIBATIV possibly related to the drug.

	VIBATIV (N=751)	Vancomycin (N=752)
Nausea	5%	4%
Vomiting	5%	4%
Renal Failure Acute	5%	4%

OVERDOSAGE: In the event of overdosage, VIBATIV should be discontinued and supportive care is advised with maintenance of glomerular filtration and careful monitoring of renal function. The clearance of telavancin by continuous venovenous hemofiltration (CVVH) has not been evaluated in a clinical study.

Manufactured by:
Theravance Biopharma Antibiotics, Inc.

Marketed by:
Theravance Biopharma US, Inc.
South San Francisco, CA 94080

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**Theravance
Biopharma** 
Medicines That Make a Difference™

Screen cut latent TB rate among immigrants

BY MARY ANN MOON
Frontline Medical News

A new approach to screening has improved detection of tuberculosis in people applying to move to the United States, according to a report in *Annals of Internal Medicine*.

The previous preimmigration screening process involved chest

radiography and, for those with abnormal radiographs, acid-fast bacilli smears of three consecutive sputum samples. If at least one smear was positive, the patient completed TB treatment overseas and was followed up after arrival in the United States. This approach failed, however, to detect some latent cases of TB that became reactivated soon after immigrants arrived in the United States.

arrived immigrants and refugees was relatively constant, at approximately 1,500/year. That number dropped to 940 cases/year after the new screening method was implemented. The number of smear-negative but culture-positive TB cases diagnosed overseas among people bound for the United States increased from 4 to 629 cases per year, the researchers said (*Ann. Intern. Med.* 2015 March 17 [doi:10.7326/M14-2082]).

Expanding screening to cover exchange visitors and temporary workers from countries with a high incidence of TB might further reduce the disease rate in foreign-born populations, the researchers concluded.

VITALS

Key clinical point: A new screening program reduced tuberculosis cases among people immigrating to the United States.

Major finding: The mean annual number of latent TB cases among newly arrived immigrants and refugees went from 1,500 before the screening program to 940 after the program was implemented.

Data source: A cross-sectional analysis of TB cases among 3,212,421 immigrants and refugees.

Disclosures: This study was supported by the Centers for Disease Control and Prevention. Mr. Liu and his associates had no disclosures.

The screening process also includes *Mycobacterium tuberculosis* culture results. For those who have at least one positive sputum smear or culture result, drug-susceptibility testing is done and directly observed therapy for TB is typically completed overseas before U.S. relocation is allowed, Yecai Liu, a mathematical statistician with the division of global migration and quarantine, Centers for Disease Control and Prevention, and his associates said.

To assess the effectiveness of the new screening algorithm, the researchers analyzed information in the CDC's disease notification database and the Department of Homeland Security's immigration records regarding 3,212,421 immigrants and refugees who were screened overseas and arrived in the United States during a 7-year period. A total of 51.4% were screened by the old method and 48.6% by the new method.

Before the new screen was implemented, the annual number of smear-negative TB cases among newly

SYMBICORT 160/4.5 for the maintenance treatment of COPD

REV THE FEV₁

SYMBICORT offers something extra—sustained* control with better breathing starting within 5 minutes each time¹⁻³

- ▶ SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- ▶ Mean percent change from baseline in FEV₁ was measured at day of randomization, months 6 and 12³

FAST CONTROL

Majority of FEV₁ improvement at 5 minutes each time¹ in a subset of SUN Study patients taking SYMBICORT 160/4.5 (n=121)^{1,4}

SUSTAINED EFFECT

SYMBICORT 160/4.5 significantly improved 1-hour postdose FEV₁ at 1 month and end of treatment compared to placebo, and improved predose FEV₁, averaged over the course of the study compared to placebo and formoterol, coprimary endpoints¹

REASSURING SENSE OF CONTROL

- ▶ The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

*Sustained improvement in lung function was demonstrated in a 12-month efficacy and safety study.

¹In a serial spirometry subset of patients taking SYMBICORT 160/4.5 (n=121) in the SUN Study, 67% of 1-hour postdose FEV₁ improvement occurred at 5 minutes on day of randomization, 83% at month 6, and 84% at end of treatment.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

▶ **WARNING:** Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients

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

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

Symbicort
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol

Meta-analysis: Oseltamivir shortens time to flu relief

BY SHARON WORCESTER
Frontline Medical News

Oseltamivir treatment in adults with influenza shortens the time to clinical symptom alleviation by

about 1 day and substantially reduces the risk of lower respiratory tract complications and hospitalization, according to a meta-analysis of randomized, controlled trials involving 4,328 adults. The findings of the study, which

is the first to use individual patient data to evaluate the neuraminidase inhibitor, should put to rest persistent doubts about its efficacy and safety, said Dr. Arnold S. Monto of the University of Michigan School of Public

Health, Ann Arbor, and his colleagues.

The intention-to-treat population of 1,591 patients with confirmed influenza had a significant 21% shorter time to clinical symptom alleviation, compared with the intention-to-treat

SYMBICORT 160/4.5 for the maintenance treatment of COPD

FAST CONTROL AT 5 MINUTES EACH TIME

Percent of 1-hour improvement in FEV₁ occurring at 5 minutes over the 12-month study⁴
(serial spirometry subset)



SUN: A 12-month efficacy and safety study

- ▶ In the SUN Study, a majority of 1-hour postdose FEV₁ improvement was seen at 5 minutes each time in a subset of patients taking SYMBICORT 160/4.5.⁴
- ▶ SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

SUN: A 12-month efficacy and safety study. A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=494), SYMBICORT pMDI 80/4.5 mcg (n=494), formoterol 4.5 mcg (n=495), and placebo (n=481), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 12-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV₁ and in 1-hour postdose FEV₁. The prespecified primary comparisons for predose FEV₁ were vs placebo and formoterol and the primary comparison for 1-hour postdose was vs placebo.

COMPARATOR ARMS: Mean improvement in 1-hour postdose FEV₁ (mL%) over 12 months (serial spirometry subset). Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%). 6 Months: SYMBICORT 160/4.5 mcg (270 mL/28%), formoterol 4.5 mcg (200 mL/23%), placebo (60 mL/7%). End of month 12 (LOCF): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol (4.5 mcg: 170 mL/19%), placebo (30 mL/5%). SYMBICORT 160/4.5 mcg[‡] (n=121), formoterol 4.5 mcg[‡] (n=124), placebo[‡] (n=125).

*Baseline is defined as the predose FEV₁ value on the day of randomization.

[†]Month 12, last observation carried forward (LOCF).

[‡]Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING (continued)

- ▶ SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- ▶ SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- ▶ Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- ▶ Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- ▶ Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids
- ▶ Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- ▶ It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids
- ▶ Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- ▶ As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- ▶ Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- ▶ Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- ▶ Long-term use of orally inhaled corticosteroids may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- ▶ Orally inhaled corticosteroids may result in a reduction in growth velocity when administered to pediatric patients
- ▶ Glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.

infected population of 1,302 patients who received placebo (97.5 hours vs. 122.7 hours; time ratio, 0.79).

The effects were somewhat attenuated in the 2,402 treated patients in the overall intention-to-treat population – with a 15% reduction in time to symptom alleviation – compared with the 1,926 placebo patients in

that population. But the difference remained significant (median of 17.8 hours; time ratio, 0.85), the investigators said (Lancet 2015 Jan. 30 [doi:10.106/S0140-6736(14)62449-1]).

The risk of lower respiratory tract complications occurring more than 48 hours after randomization was 4.2% in oseltamivir-treated patients

and 8.7% in those who received placebo, a 44% difference. The risk of hospitalization for any cause was 0.6% vs. 1.7%, a reduction of 63%.

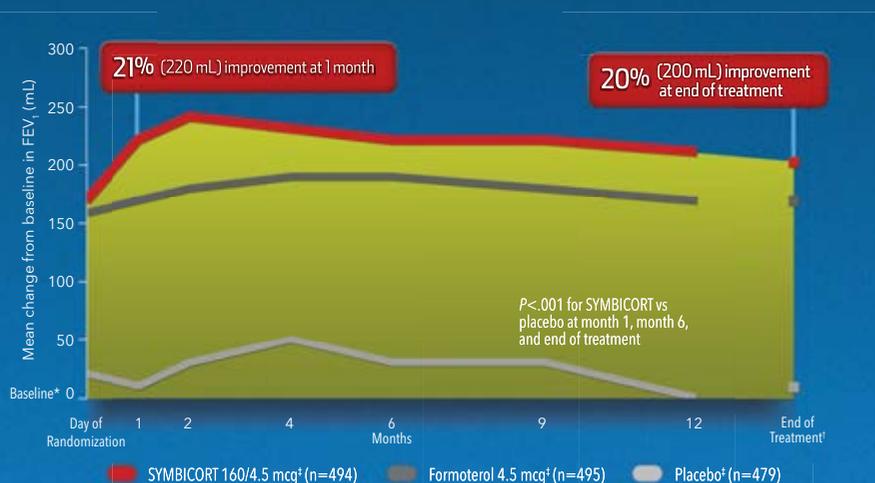
The researchers included all published and unpublished Roche-sponsored randomized, placebo-controlled, double-blind trials of the standard prescribed oseltamivir dose of 75 mg

twice daily in adults. Patients were within 36 hours of feeling unwell, had a fever and at least one respiratory and one constitutional symptom.

The Multiparty Group for Advice on Science funded the study via an unrestricted grant from Roche. Dr. Monto reported receiving fees from Roche outside of the submitted work.

SUSTAINED EFFECT OVER 12 MONTHS

Improvement in 1-hour postdose FEV₁ over the 12-month study⁴



SYMBICORT IS ON
EXPRESS SCRIPTS[®]
NATIONAL PREFERRED
FORMULARY
INDICATED
FOR BOTH COPD AND ASTHMA,
IN APPROPRIATE PATIENTS^{§§}

SUN: A 12-month efficacy and safety study

► SYMBICORT 160/4.5 significantly improved 1-hour postdose FEV₁ at 1 month and end of treatment compared to placebo, and improved predose FEV₁ averaged over the course of the study compared to placebo and formoterol, coprimary endpoints¹

COMPARATOR ARMS: Mean improvement in 1-hour postdose FEV₁ (mL/%) over 12 months. **Month 1:** SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%). **Month 6:** SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (190 mL/18%), placebo (30 mL/3%). **End of treatment:** SYMBICORT 160/4.5 mcg (200 mL/20%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%). **SYMBICORT 160/4.5 mcg[†] (n=494), formoterol 4.5 mcg[‡] (n=495), placebo[§] (n=479).**

*Baseline is defined as the predose FEV₁ value on the day of randomization.

[†]Month 12, last observation carried forward.

[‡]Administered as 2 inhalations twice daily.

SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts

- In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma

- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

- SYMBICORT is indicated for the treatment of asthma in patients 12 years and older (also see Boxed WARNING)
- SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
- SYMBICORT is NOT indicated for the relief of acute bronchospasm

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. 2. SYMBICORT [package insert]. Wilmington, DE: AstraZeneca; 2012. 3. Data on File, 273071, AZPLP. 4. Data on File, 1084400, AZPLP. 5. 2014 Express Scripts Preferred Drug List.

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AstraZeneca

Symbicort
(budesonide/formoterol fumarate dihydrate)
Inhalation Aerosol
A reassuring sense of control

Everolimus-eluting stents linked to higher MI risk

BY **BIANCA NOGRADY**
Frontline Medical News

Percutaneous coronary intervention with second-generation everolimus-eluting stents is asso-

ciated with a similar risk of death but a higher risk of myocardial infarction and repeat revascularization than is coronary artery bypass grafting.

An observational registry study of 34,819 patients with multivessel cor-

onary artery disease who underwent one or the other procedure showed a similar risk of death at a mean follow-up of 2.9 years between patients who underwent PCI with everolimus-eluting stents and those who un-

derwent CABG (3.1% and 2.9% per year, hazard ratio, 1.04; $P = .50$).

However, those in the percutaneous coronary intervention group had a 51% greater risk of MI (95% confidence interval, 1.29-1.77; $P < .001$).

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

For Oral Inhalation Only
Rx only

WARNING: ASTHMA RELATED DEATH

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

BRIEF SUMMARY

Before prescribing, please see full Prescribing Information for SYMBICORT® (budesonide/formoterol fumarate dihydrate).

INDICATIONS AND USAGE

Treatment of Asthma

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

Long-acting beta₂-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients [see WARNINGS AND PRECAUTIONS]. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitations of Use:

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

Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

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

Important Limitations of Use: SYMBICORT is not indicated for the relief of acute bronchospasm.

DOSAGE AND ADMINISTRATION

SYMBICORT should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing [see PATIENT COUNSELING INFORMATION in full Prescribing Information (17.4)].

Prime SYMBICORT before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing two test sprays into the air away from the face.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT is not recommended as some patients are more likely to experience adverse effects with higher doses of formoterol. Patients using SYMBICORT should not use additional long-acting beta₂-agonists for any reason [see WARNINGS AND PRECAUTIONS].

Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart).

The recommended starting dosages for SYMBICORT for patients 12 years of age and older are based upon patients' asthma severity.

The maximum recommended dosage is SYMBICORT 160/4.5 mcg twice daily.

Improvement in asthma control following inhaled administration of SYMBICORT can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacement with SYMBICORT 160/4.5 may provide additional asthma control.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, (e.g., replacing the lower strength of SYMBICORT with the higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids) should be considered.

Chronic Obstructive Pulmonary Disease (COPD)

For patients with COPD the recommended dose is SYMBICORT 160/4.5, two inhalations twice daily.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

Long-acting beta₂-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

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

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

Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta₂-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting beta₂-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

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

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

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

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Patients should rinse the mouth after inhalation of SYMBICORT.

Pneumonia and Other Lower Respiratory Tract Infections

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

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

Immunosuppression

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

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

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

Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

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

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

Hypercorticism and Adrenal Suppression

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

VITALS

Key clinical point: PCI with second-generation everolimus-eluting stents is associated with a similar risk of death but a higher risk of MI and repeat revascularization than does CABG.

Major finding: PCI was associated with a 51% greater risk of MI at 2.9 years of follow-up, compared with CABG.

Data source: An observational registry study of 34,819 patients with multivessel coronary artery disease.

Disclosures: The study was supported by Abbott Vascular. Dr. Bangalore has received consultant fees or honoraria from Abbott Vascular, Boehringer Ingelheim, Daiichi Sankyo, Gilead Sciences, Pfizer, and Unique Pharmaceuticals.

This increase in risk was significant only in patients who had incomplete revascularization and not in those with complete revascularization. Also, the increase in risk largely was tied to spontaneous MI.

“Trials comparing PCI with CABG have not been typically powered to evaluate differences in the rates of myocardial infarction, stroke, and death from any cause; instead, they have been

Continued on page 21

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

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

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

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

Cardiovascular and Central Nervous System Effects

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

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

Reduction in Bone Mineral Density

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

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see **DOSE AND ADMINISTRATION** and **USE IN SPECIFIC POPULATIONS**].

Glaucoma and Cataracts

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

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

Eosinophilic Conditions and Churg-Strauss Syndrome

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

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

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see **WARNINGS AND PRECAUTIONS**].

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection [see **WARNINGS AND PRECAUTIONS**]
- Pneumonia or lower respiratory tract infections in patients with COPD [see **WARNINGS AND PRECAUTIONS**]
- Immunosuppression [see **WARNINGS AND PRECAUTIONS**]
- Hypercorticism and adrenal suppression [see **WARNINGS AND PRECAUTIONS**]
- Growth effects in pediatric patients [see **WARNINGS AND PRECAUTIONS**]
- Glaucoma and cataracts [see **WARNINGS AND PRECAUTIONS**]

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

Clinical Trials Experience in Asthma

Patients 12 years and older

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

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

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

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

* All treatments were administered as two inhalations twice daily.

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

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

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

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

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

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

* All treatments were administered as two inhalations twice daily.

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

Postmarketing Experience

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

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

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea

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

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor, dizziness

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

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

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

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

Cardiovascular event rates similar in PCI and CABG

BY **BIANCA NOGRADY**
Frontline Medical News

Percutaneous coronary intervention with a sirolimus-eluting stent showed comparable

rates of death, myocardial infarction and stroke to coronary artery bypass grafting in patients with coronary artery stenosis after 5 years in a randomized trial.

The PRECOMBAT (Premier of

Randomized Comparison of Bypass-Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) study randomized trial in 600 patients with unprotected left main coronary

VITALS

Key clinical point: Percutaneous coronary intervention with sirolimus-eluting stents shows comparable rates of death, myocardial infarction, and stroke to coronary artery bypass grafting after 5 years.

Major finding: There were no significant differences in major adverse cardiac or cerebrovascular events between PCI and CABG in patients with unprotected left main coronary artery stenosis.

Data source: PRECOMBAT, a randomized trial in 600 patients with unprotected left main coronary artery stenosis.

Disclosures: The study was supported by the CardioVascular Research Foundation, Cordis, Johnson & Johnson, and the Korean Ministry of Health & Welfare. No conflicts of interest were disclosed.

artery stenosis – 300 of whom were randomized to PCI and the rest to CABG – showed no significant difference in major adverse cardiac or cerebrovascular events (hazard ratio, 1.27; 95% confidence interval, 0.84-1.90; $P = 0.26$), according to a presentation at the American College of Cardiology meeting in San Diego.

However, the study did observe a twofold increase in the rate of ischemia-driven target vessel revascularization among patients treated with PCI, compared to those who underwent CABG (HR, 2.11; 95% CI, 1.16-3.84; $P = 0.012$).

The authors pointed out that this increase in revascularization did not appear to impact the study's harder endpoints.

“Given a higher rate of repeat revascularization even after the use of second-generation drug-eluting stents for unprotected left main coronary artery stenosis, frequent repeat revascularization could be an inherent weakness of stent-related treatments,” wrote Dr. Jung-Min Ahn, from the Asan Medical Center, Seoul, and coauthors (J. Am. Coll. Cardiol. 2015; March 15 [doi:10.1016/j.jacc.2015.03.033]).

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

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Inhibitors of Cytochrome P450 3A4

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

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

Beta-Adrenergic Receptor Blocking Agents

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

Diuretics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocidal in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

SYMBICORT

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis.

Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than the maximum recommended human daily inhalation dose on a mcg/m² basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m² basis. In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 3 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Umbilical hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Brachygnathia was observed in rat fetuses at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. Pregnancy was prolonged at an oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Nonteratogenic Effects

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

Labor and Delivery

There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers

Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [see **CLINICAL PHARMACOLOGY, Pharmacokinetics** in full Prescribing Information (12.3)]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

Pediatric Use

Safety and effectiveness of SYMBICORT in asthma patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily [see **CLINICAL STUDIES** in full Prescribing Information (14.1)]. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established.

Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see **DOSE AND ADMINISTRATION**].

Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4.5 twice daily were 65 years old and above and of those, 73 patients were 75 years of age and older. No overall differences in growth or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing beta₂-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists.

Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

Hepatic Impairment

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

Renal Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment.

OVERDOSAGE

SYMBICORT

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

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

Budesonide

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

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

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta₂-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

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

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

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PCI linked to higher rate of cardiovascular events

BY **BIANCA NOGRADY**
Frontline Medical News

SAN DIEGO – Percutaneous coronary intervention with everolimus-eluting stents is associated with significantly higher major adverse cardiovascular events than is coronary artery bypass grafting in patients with multivessel coronary artery disease, according to results of the BEST trial.

In the randomized noninferiority trial of 880 patients, there was a 47% higher rate of the primary endpoint of death, myocardial infarction, or target vessel revascularization among patients randomized to percutaneous coronary intervention with the new-generation drug-eluting stent than among those randomized to coronary artery bypass grafting, after a median of 4.6 years follow-up.

However, the differences in primary endpoint were not significant for noninferiority between the two groups at the 2-year follow-up mark, Dr. Seung-Jung Park said at the annual meeting of the American College of Cardiology.

The Xience everolimus-eluting stent used in BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease) is one of several bioabsorbable vascular scaffolds that have caught on in recent years. The working hypothesis behind the device is that by dissolving during a period of 12-24 months, the scaffold provides temporary bracing against restenosis but then disappears, allowing improved endovascular healing.

Patients were randomized after diagnostic coronary angiography to PCI (438 patients) or to CABG (442).

The study, which was terminated early because of slow enrollment, also found a significantly greater rate of the composite secondary endpoint of death, myocardial infarction, stroke, or repeat revascularization in the PCI group compared to the CABG group (19.9% vs. 13.3%, $P = .01$).

There were no significant differences between the two groups in the rate of the other secondary safety endpoint: a composite of death, MI, and stroke.

In total, 29 patients assigned to PCI died, compared with 22 assigned to CABG (6.6% vs. 5%, $P = .30$).

The rate of spontaneous myocardial infarction was significantly higher in the PCI group (4.3% vs. 1.6%, $P = .02$), as was the rate of repeat revascularization (11% vs. 5.4%, $P = .003$).

There were fewer incidences of major bleeding in the PCI group compared to the CABG group, although the rate of fatal major bleeding was similar for both arms of the study.

Diabetes status had a major negative impact on outcome for patients undergoing PCI, increasing the rate of the primary endpoint to 19.2%, compared to 9.1% in patients undergoing CABG ($P = .007$).

“In the BEST trial, PCI with everolimus-eluting stents was not shown to be noninferior to CABG with respect to the primary endpoint of death, myocardial infarction, or target vessel revascularization at 2 years,” wrote Dr. Park of the University of Ulsan (South Korea) College of Medicine, and his coauthors.

Within 30 days of the procedure, patients who underwent PCI showed lower risk of death and stroke but no significant differences in MI risk.

“Thus, the choice between CABG and PCI with everolimus-eluting stents may depend on whether complete revascularization can be achieved with PCI,” the authors wrote. “If the answer is yes, the choice between PCI and CABG should be made on the basis of weighing the short-term risk of death and stroke against the long-term risk of revascularization with PCI.”

The authors acknowledged the study was a nonrandomized, observational trial; it did not examine smoking and other comorbidities; and it did not capture neurologic events such as transient ischemic attack.

The article was published online simultaneously with his presentation (N. Engl. J. Med. 2015 March 15 [doi:10.1056/NEJMoa1415447]).

“At longer-term follow-up (median 4.6 years), PCI was associated with a significant increase in the incidence of the primary endpoint, as compared to the incidence with CABG.”

The authors suggested this difference was largely attributable to the higher rate of repeat target vessel revascularization in patients who had undergone PCI, as well as the spontaneous myocardial infarction and new lesion revascularization.

In contrast to previous studies, the researchers did not find a significant difference in the rate of stroke between the two groups.

“The reason for this discrepancy

is not clear, but the use of off-pump CABG can avoid excessive manipulation of the aorta, and may have contributed to a reduced rate of stroke in the CABG group in our study,” the authors noted.

The researchers acknowledged that the trial was not powered to detect differences in individual endpoints and that they did experience enrollment difficulties.

The CardioVascular Research Foundation, Abbott Vascular, and the Korea Healthcare Technology Research and Development Project supported the study. Dr. Park disclosed ties with Abbott, Cordis, Boston Scientific, and Medtronic, and has an ownership interest in the Cardiovascular Research Foundation.

VIEW ON THE NEWS

PCI and CABG as complementary rather than competitive interventions

Dr. G. Hossein Almassi, FCCP, comments:

These three studies presented at the American College of Cardiology meeting in San Diego compare PCI to CABG in patients with multivessel coronary artery disease. Both the randomized trial from Ulsan (South Korea) University (the BEST trial) and the observational study from New York used the newer generation everolimus-eluting stent. The primary endpoints of myocardial infarction and repeat revascularization were higher in the PCI group in both studies and, even more so in patients with diabetes in the BEST trial. The third study, the PRECOMBAT trial (Asan, Korea), was a randomized trial, comparing PCI using a sirolimus-eluting stent in patients with unprotected left main coronary disease. The outcomes at 5 years were similar to those of CABG, although the rate of ischemia-driven revascularization was twofold higher in the PCI group.

The Achilles heel of CABG in all the trials has been a higher rate of stroke at the initial hospitalization. Using a no touch aortic technique, the Ulsan group did not find a difference in the stroke rate between the PCI and the CABG groups.

CABG is a Class 1 indication for



patients with left main stenosis, multivessel CAD and especially in those with left ventricular dysfunction and in diabetic patients (2011, ACCF/AHA guidelines). The seminal SYNTAX trial concluded that “CABG, as compared with PCI, is associated with a lower rate of major adverse cardiac or cerebrovascular events at 1 year among patients with three-vessel or left main coronary artery disease (or both) and should therefore remain the standard of care for such patients (N. Engl. J. Med. 2009;360:961-72).

SYNTAX also established the concept of a cardiac team including a cardiologist and a cardiac surgeon for the treatment of patients with CAD, a concept that is now being applied to patients undergoing percutaneous aortic valve implantation (TAVI or TAVR). This is now a Class 1 indication based on the 2011 ACCF/AHA CABG guidelines. Implementation of a cardiac team approach will lead to a paradigm shift in the treatment of CAD where PCI and CABG are implemented as complementary rather than competitive treatment modalities applied to patients with CAD as appropriate and based on patient’s coronary anatomy (SYNTAX score) and clinical profile (STS score).

Continued from page 19

based on composite outcomes that include repeat revascularization,” wrote Dr. Sripal Bangalore of New York University and coauthors.

Patients undergoing PCI with everolimus-eluting stents also had a greater than twofold increase in the risk of repeat revascularization (hazard ratio, 2.35; 95% CI, 2.14-2.58; $P < .001$), particularly in patients with three-vessel disease.

However, those in the PCI group also had a 58% lower risk of stroke than did those in the CABG group (95% CI, 0.50-0.76; $P < .001$), which was driven largely by a reduced risk in the first 30 days after the procedure (N. Engl. J. Med. 2015 March 16 [doi:10.1056/NEJMoa1412168]).

CRITICAL CARE COMMENTARY: Bed management – can we do better?

BY DR. MICHAEL J. WAXMAN,
MBA, FCCP

Is it possible to give the best critical care while spending less money and resources doing it? Can we reduce waste while improving quality in a so-called lean approach to critical care? I believe that we have too many critical care beds, and we fill some of those beds with patients who can be taken care of at less intense levels of care—which are also less expensive.

Most work that is done to improve critical care looks at the quality of care. This is an area where a lot of data are accumulating. Take septic shock, for example. In the recently published ProCESS trial (The ProCESS Investigators. *N Engl J Med.* 2014; 370[18]:1683), the 60-day in-hospital mortality for septic shock was 18.2 to 21.0%. A lot of institutions (including mine) are struggling to get their septic shock mortality rate under 30%. Although some people critique the ProCESS trial mortality rate on patient selection, most of us try to figure out how to duplicate that lower rate. We do this in areas other than septic shock. If we are comparable in whatever quality statistic, we applaud our success. If we aren't comparable, we look at ways to improve, often based on what was done in that particular study.

How big of a financial burden is our critical care spending? According to an analysis of critical care beds by Halpern and colleagues (*Crit Care Med.* 2004;32[6]:1254), the number of hospital beds decreased

26.4% between 1985 and 2000, and the absolute number of critical care beds increased 26.2% (quantitated at 67,357 adult beds in 2007 per SCCM.org (www.sccm.org/Communications/Pages/CriticalCareStats.aspx). Critical care beds cost \$2,674 per day in 2000, up from \$1,185 (our CFOs tell us it is more like \$3,500 to \$4,000 per day now). They represented 13.3% of hospital costs, 4.2% of national health expenditures (NHE), and 0.56% of gross domestic product (GDP). There are 55,000 critically ill patients cared for each day in the United States, representing 5 million ICU patients per year. This is an enormous expenditure of money and it is growing.

Another interesting observation by Halpern and colleagues (*Crit Care Med.* 2004;32[6]:1254), was that critical care beds were only at 65% occupancy. This reflects my own experience where we operate at a 70% average ICU bed occupancy. We have created a larger financial burden with the fixed costs of one third more ICU beds than we actually use. Some bed availability is desirable, but how much is too much?

Are we doing the best job to give quality care and spend money wisely? Can we be more efficient in the throughput of patients and in their care? Admission criteria should be part of any unit, designed to place all patients who need ICU care appropriately in the ICU and exclude those whose care can be managed at a lesser level of intensity and cost. Discharge criteria, care protocols (eg, wake up and wean), checklists, and



DR. WAXMAN

EDITOR'S COMMENTS

What is the ideal number of ICU beds for any given hospital? Which criteria should be used to determine who gets those beds? Who is the best gatekeeper to equitably allow admission to the ICU? And is there an app for that? The “right” answers to these questions vary depending on who is providing you with the answer key.

In the current *Critical Care Commentary*, Dr. Mike Waxman begins to unravel these complex issues and challenges us to do more with less. The data are clear that the ratio of ICU beds to general ward beds in US hospitals is markedly increased compared with other developed countries—and that we fill those beds with patients of lower acuity. Our epidemiology colleagues have made several other troubling observations of late: ICU admissions are growing fastest in patients aged 85 and older; most admissions from the ED are for symptoms—think chest pain or shortness of breath—that can signal a life-threatening condition but are more likely due to other problems, and the utilization of advanced imaging prior to ICU transfer has more than doubled in recent years. These findings sug-



gest that factors such as changing demographics and medical-legal concerns are working against our “lean” approach to ICU care.

Equally troubling, many patients and non-ICU clinicians now view the hospital's general ward vs ICU bed designation on par with an airline gate agent's coach vs business class seat assignment. Through their eyes, patients receive more attention (2:1 nurse staffing and 24/7 in-house coverage anyone?) and more monitoring (Ah, I see you have the machine that goes “ping”) behind the velvet ropes of the ICU. Lost from their view, buried deep in the bowels of the electronic medical record, is the fact that three times as many dollars are spent on their care without any incremental benefit. Sadly, many cost-conscious intensivists who attempt to use evidence-based criteria for ICU triage are steamrolled into submission by such misinformed clinicians and/or administrators under the misplaced auspices of patient safety. Hopefully, innovators such as Dr. Waxman will succeed in moving the needle and transform our JICU (just-in-case unit) beds back to ICU beds.

Dr. Lee E. Morrow, FCCP

daily attention to the usual parameters (eg, DVT prophylaxis) are essential for high quality but efficient care. Done 24/7, we can maximize efficiency and quality with a minimum of ICU readmissions. Throughput is part of every physician's job description. The physician who wants one more day for his or her patient in the ICU simply because the nurse has fewer patients misses a number of points. Why would anyone want more exposure to resistant organisms, more noise, more awakenings, and less sleep, just to name a few? Keeping that non-ICU patient in the ICU bed might even delay the transfer of another patient coming from the ED, where we know they often don't get good ICU care.

Are the beds filled only with what we intensivists would consider legitimate ICU patients, defined by both generally accepted (endotracheal tube in place) and individually specified criteria (unit specific related to other unit capabilities)? That would

impact cost. An interesting article by Gooch and Kahn (*JAMA.* 2014; 311[6]:567) discussed the demand elasticity of the ICU. They considered the changes in case mix of patients between days of high and low bed availability. They contended that when ICU beds were available, there was an increase in patients who were unlikely to benefit from ICU admission. This group included a population of patients likely to survive and whose illness severity was low and a population of patients who were unlikely to survive and had a high illness severity. In other words, admissions expand to fill the staff-able beds. If this is true, it is another area where better management could lower costs without reducing the quality of care.

What if bed availability truly is reduced, often by a lack of critical care nursing staff if not physical beds? Here the answer is unclear. Town (*Crit Care Med.* 2014;42[9]:2037) looked at ICU readmission rates and

Continued on following page



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the odds of having a cardiac arrest on the ward related to bed availability. Five ICUs with 63 beds total were examined. As ICU bed availability decreased, the odds of patients who were discharged from the ICU being readmitted to the ICU went up. Also, the odds of patients having a cardiac arrest on the ward increased when medical (not total) ICU beds were less available. In 2013, Wagner and colleagues (*Ann Intern Med.* 2013;159[7]:447) looked at 155 ICUs with 200,730 patients discharged from ICUs to hospital floors from 2001 to 2008. They examined what they call the strain metrics. These included the standardized ICU census, the proportion of new admissions, and the average predicted probability of death of the other patients in the ICU on the days of ICU discharge. When the strain metrics increased, ICU patients had shorter ICU length of stay and ICU readmission odds went up. They didn't, however, see an increased odds of death, a reduced odds of being discharged home, or a longer total hospital LOS. In a third study reported in 2008 in the *Annals of Internal Medicine* by Howell and colleagues (*Ann Intern Med.* 2008;149[11]:804), an innovative method of bed management was described. Because of an overcrowded ED and a high ambulance diversion rate, hospitalists implemented a system of bed control that was based on knowledge of ICU beds and ED congestion and flow. Bed assignments were better controlled by twice-daily ICU rounds and regular visits to the ED: throughput for admitted patients decreased by 98 min and time on diversion decreased significantly.

Mery and Kahn reported in 2013 (*Crit Care.* 2013;17[3]:315) that when ICU bed availability was reduced, there was a reduction in the likelihood of ICU admission within 2 h of a medical emergency team (MET) activation. What is interesting about this study done in three hospitals in Calgary, Alberta, Canada, is that there was an increased likelihood that the patient goals of care changed to comfort care when there was no bed availability compared with two ICU beds being available. Even more interesting is that hospital mortality did not vary significantly by ICU bed availability: more patients were moved to palliative care yet no more people died. Perhaps a lack of ICU beds expedited appropriateness of care.

To summarize, we have more patients in critical care beds where we spend ever-increasing amounts of

our health-care dollars, but we seem to have more critical care beds than we need. We still have patients in our ICUs who would be better cared for elsewhere in our institutions. We can perform more cost-effective throughput when we are pressed to do so and usually we can do it safely.

I contend that the next improve-

ment in lean ICU medicine will be better management tools. Comprehensive checklists help me where computer solutions have yet to be developed.

I am working to create hardware/software management solutions to make my job more cost-effective and to provide a sustainable process

for what comes after me.

Dr. Waxman is Associate Professor of Medicine, KU School of Medicine, Kansas City, Kansas; Medical Director, Medical Surgical ICU/PCU, Research Medical Center; and Adjunct Professor, Rockhurst University, Helzberg School of Management, Kansas City, Missouri.

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Elevated Liver Enzymes

- The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment.
- In clinical trials, administration of OFEV 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 (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

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



OFEV[®]
(nintedanib)
capsules 150mg

Fresh RBCs add no advantages for critically ill

BY **BIANCA NOGRADY**
Frontline Medical News

The use of fresh red blood cells for transfusion did not reduce mortality or improve other

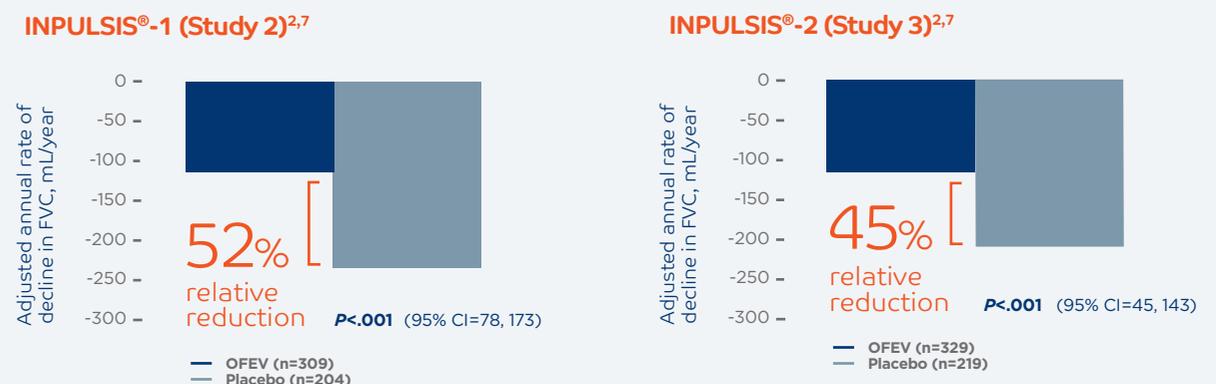
outcomes, compared with older red cells, based on a multicenter, blinded, randomized prospective study presented at the annual meeting of the International Society on Intensive Care and Emergency Medicine.

In the Age of Blood Evaluation (ABLE) study, researchers randomized 1,211 critically ill patients to red blood cells stored for less than 8 days and 1,219 patients to standard-issue cells stored for a mean of 22.4 days.

The study was conducted at 64 centers in Europe and Canada, where all blood units were leukoreduced and SAGM (saline-adenine-glucose-mannitol) suspended. Similar products are
Continued on page 26

The totality of the evidence demonstrates that OFEV slows IPF progression²⁻⁶

REPRODUCIBLE REDUCTIONS IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 TRIALS^{2*}



• -115 mL/year for OFEV (nintedanib) compared with -240 mL/year for placebo*

• -114 mL/year for OFEV compared with -207 mL/year for placebo*

TOMORROW (Study 1): OFEV demonstrated a 68% relative reduction in the annual rate of FVC decline compared with placebo (-60 mL/year vs -191 mL/year, respectively; $P=.01$, 95% CI=27, 235)^{2,8}

OFEV SIGNIFICANTLY REDUCED THE RISK OF FIRST ACUTE IPF EXACERBATION OVER 52 WEEKS COMPARED WITH PLACEBO IN 2 OUT OF 3 CLINICAL TRIALS²

• **INPULSIS®-2** (adjudicated): HR=0.20 (95% CI=0.07, 0.56); **TOMORROW** (investigator-reported): HR=0.16 (95% CI=0.04, 0.71); **INPULSIS®-1** (adjudicated): HR=0.55 (95% CI=0.20, 1.54; not statistically significant)

CI, confidence interval; HR, hazard ratio.

*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.²

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. 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 modifications 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. 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.

VITALS

Key clinical point: Fresh red blood cells didn't provide any additional gains in outcomes or reduce mortality at 90 days.

Major finding: The survival analysis of the time to death showed a hazard ratio of those in the fresh-blood group was

1.1, compared to those in the standard blood group (95% confidence interval, 0.9-1.2) ($P = .38$).

Data source: A multicenter, blinded, randomized prospective study in 2,430 patients receiving red blood cell transfusions.

Disclosures: The study was supported by the Canadian Institutes of Health Research, Fonds de Recherche du Québec-Santé, the National Institute for Health Research Evaluation, the French Ministry of Health, and the Etablissement Français du Sang, and

Sanquin Blood Supply. Two authors reported grants and personal fees from pharmaceutical companies outside the submitted work, while others reported financial support from the study funding sources.

The safety and tolerability of OFEV was demonstrated in 3 clinical trials²

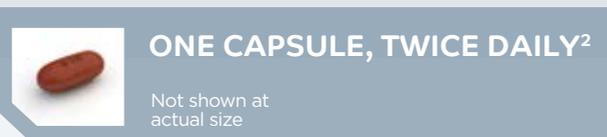
THE MOST COMMON ADVERSE EVENTS WERE GASTROINTESTINAL IN NATURE AND GENERALLY OF MILD OR MODERATE INTENSITY²

- Diarrhea was reported in 62% of patients receiving OFEV vs 18% on placebo
- Diarrhea can be managed by symptomatic treatment, dose reduction, or treatment interruption until diarrhea resolves to levels that allow continuation of therapy. If severe diarrhea persists despite symptomatic treatment, discontinue OFEV

OFEV OFFERS TWICE-DAILY ORAL DOSING²

- Conduct liver function tests prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated
- OFEV capsules should be taken 12 hours apart, with food, and should be swallowed with a glass of water. OFEV capsules should not be chewed or crushed because of a bitter taste. If a dose is missed, treatment should resume at the next scheduled time and at the recommended dose. Do not exceed the recommended maximum daily dosage of 300 mg
- In addition to symptomatic treatment, temporary dose reduction (100 mg twice daily) or treatment interruption should be considered for management of adverse reactions until the reaction resolves to levels that allow continuation of therapy. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV
- For AST or ALT >3 times to <5 times the ULN without signs of severe liver damage, interrupt treatment or reduce dose to 100 mg. Once levels return to baseline values, OFEV may be reintroduced at a reduced dosage (100 mg BID), which may be increased to the full dosage. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.



IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Embryofetal Toxicity

- OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

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.

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



Continued from page 24

supplied in the United States, but red cells are suspended in additive solution 3 (AS3) rather than SAGM.

At 90 days, 37% of patients in the fresh-blood group and 35% of patients in the standard blood group had died. The survival analysis of the

time to death showed a hazard ratio of those in the fresh-blood group was 1.1, compared with those in the standard blood group (95% confidence interval, 0.9-1.2; $P = .38$). There were no differences in death rate, organ failure, acute respiratory distress, cardiac complications, thrombosis, infection, or acute transfusion reaction.

There were no differences in length of hospital stay or duration of supportive care such as mechanical ventilation.

“Although [other] initial studies showed an association between longer red-cell storage and adverse outcomes, these associations may have been spurious owing to sicker patients receiving more units with

longer storage, the overlap between comparison groups in the age of the red cells transfused, and the inclusion of transfusions that occurred after the clinical events,” Dr. Jacques Lacroix of University of Montreal and his coauthors wrote in the March 17 edition of the *New England Journal of Medicine* (doi:10.1056/NEJMoa1500704).

OFEV is available through participating specialty pharmacies



COMPLETE the OFEV (nintedanib) Prescription Form, available at www.OFEV.com



FAX the completed form to one of our 4 partnering specialty pharmacies



Acro Pharmaceutical Services
Phone: 800-906-7798
Fax: 855-439-4768



Advanced Care Scripts
Phone: 855-252-5715
Fax: 866-679-7131



Orsini Healthcare
Phone: 800-372-9581 (option 3)
Fax: 888-975-1456



Walgreens
Phone: 800-420-3228
Fax: 866-889-1510

IMPORTANT SAFETY INFORMATION ADVERSE REACTIONS

- Adverse reactions reported in $\geq 5\%$ of patients treated with OFEV and more commonly than in patients treated with placebo included diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs. 6%), liver enzyme elevation (14% vs. 3%), vomiting (12% vs. 3%), decreased appetite (11% vs. 5%), weight decreased (10% vs. 3%), headache (8% vs. 5%), and hypertension (5% vs. 4%).
- 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 predefined 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.

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.

Please see brief summary for OFEV on the following pages.

References: 1. US Food and Drug Administration. [http://www.fda.gov/downloads/Regulatory Information/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsstotheFDCA/FDASIA/UCM380724.pdf](http://www.fda.gov/downloads/Regulatory%20Information/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsstotheFDCA/FDASIA/UCM380724.pdf). Accessed February 11, 2015. 2. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. 3. Zappala CJ et al. *Eur Respir J*. 2010;35(4):830-836. 4. Schmidt SL et al. *Chest*. 2014;145(3):579-585. 5. du Bois RM et al. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. 6. Song JW et al. *Eur Respir J*. 2011;37(2):356-363. 7. Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;370(22):2071-2082. 8. Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087.

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 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.

USE IN SPECIFIC POPULATIONS

Nursing Mothers

- Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic Impairment

- Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment (Child Pugh A). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended.

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.

OFHCPISIJAN15



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FDA approves filgrastim as first 'biosimilar' in US

BY ELIZABETH MEHCATIE
Frontline Medical News

A biosimilar version of filgrastim, the leukocyte growth factor marketed as Neupogen, has

been approved by the Food and Drug Administration, the first approval of a biosimilar in the United States.

The filgrastim biosimilar will be marketed as Zarzio by Sandoz and is approved for the same indications

as Amgen's Neupogen, which was licensed by the FDA in 1991. There are at least four other biosimilar versions of biologic products being reviewed by the FDA, including an infliximab (Remicade) biosimilar. Biosimilars are

expected to make biological therapies available at a lower price, the FDA said.

The nonproprietary name for Zarzio is "filgrastim-sndz."

emechcatie@frontlinemedcom.com

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests 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. **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.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment [see Use in Specific Populations]. 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 modifications 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 (nintedanib). **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. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetotoxic in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of 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]; Embryofetal Toxicity [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 (nintedanib), 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 predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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

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

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

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

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

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

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

Trauma patients need more enoxaparin to halt VTEs

BY M. ALEXANDER OTTO
Frontline Medical News

PHOENIX – Trauma patients probably need an elevated dose of enoxaparin – perhaps 40 mg twice daily – to

prevent venous thromboembolisms, according to a prospective study of 85 trauma patients at the Palmetto Health Richland Hospital in Columbia, S.C.

Also, antifactor 10a – a blood test often used in research to gauge

how well enoxaparin (Lovenox) is thinning the blood – doesn't work very well as an empiric measure of anticoagulation; thromboelastography may be better, lead investigator Janise Phillips, Pharm.D.,

said at the Critical Care Congress, sponsored by the Society of Critical Care Medicine.

Her team tracked trauma patients who had at least three consecutive doses of enoxaparin prophylaxis for venous thromboembolism and at least one peak antifactor 10a level drawn; enoxaparin doses were adjusted as needed to hit a weekly antifactor 10a level of 0.20-0.40 IU/mL, which is thought to be the therapeutic range for enoxaparin.



Critically ill trauma patients – and perhaps burn patients – need higher anticoagulant doses.

DR. PHILLIPS

Patients were in the ICU for a median of about 10 days, and in the hospital for about 2-3 weeks.

The types of trauma were not reported in the study, but the investigation confirms prior findings that critically ill trauma patients – and perhaps burn patients – need higher anticoagulant doses.

Overall, 65% of patients (13) on an initial enoxaparin regimen of 30 mg subcutaneously twice daily were below anti-factor 10a levels of 0.20-0.40 IU/mL after their first dose; 22% (8) were at a subtherapeutic level after an initial dose of 40 mg once daily; and 21% (6) were at a subtherapeutic level after an initial dose of 40 mg twice daily.

Anti-factor 10a levels didn't match well with clinical benefit. VTEs were diagnosed in 15% of patients (4) with an initial subtherapeutic anti-factor 10a level, but 15% (4) bled on their subtherapeutic dose; 8.5% of patients (4) with an initial therapeutic level had a VTE, vs. none who were supratherapeutic after their initial dose. However, 9% of supratherapeutic patients (1) had an enoxaparin bleed.

"These were trauma patients in and out of surgery. A lot of the time, we had to stop the dose and hold it, which may" explain why subtherapeutic patients had the highest VTE risk, said Dr. Phillips, now a critical care pharmacist at the Cleveland Clinic hospital in Abu Dhabi, United Arab Emirates.

The fact that both VTEs and bleeding were most likely in underdosed patients could mean that anti-factor 10a "is really not the best marker for VTE risk," Dr. Phillips said.

anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category D. [See Warnings and Precautions]: OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects 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). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total 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%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, 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 (nintedanib). Advise patients that their healthcare provider may recommend hydration, anti-diarrheal 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]. **Pregnancy:** Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate 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]. **Nursing Mothers:** Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing [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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FDA approves Anthrasil to treat inhalational anthrax

BY DEEPAK CHITNIS
Frontline Medical News

The Food and Drug Administration has approved Anthrasil, Anthrax Immune Globulin Intravenous (Human), for the treatment of inhalational anthrax when used with appropriate antibacterial drugs.

Dr. Karen Midthun, director of the

Center for Biologics Evaluation and Research, said in a statement that Anthrasil “will be stored in U.S. Strategic National Stockpile to facilitate its availability in response to an anthrax emergency.”

Anthrasil was purchased by the Department of Health & Human Services’ Biomedical Advanced Research and Development Authority

(BARDA) in 2011, but because it was not approved, its use prior to FDA approval would have required an emergency use authorization from the FDA.

The efficacy of Anthrasil was studied in animals, the FDA said. The survival rate for monkeys exposed to *Bacillus anthracis* spores and then given Anthrasil was between

36% and 70%. None of the monkeys given placebo survived. Rabbits had a 26% survival rate when given the drug, compared with 2% of those given placebo. Safety was tested in 74 healthy human volunteers; the most commonly reported side effects included headache, back pain, and nausea.

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Environmental factors could increase U.S. anthrax cases

BY DEEPAK CHITNIS
Frontline Medical News

WASHINGTON – Isolated cases of anthrax in Minnesota and elsewhere, along with the disease’s relative ease of transmission from animals or plants to humans, should heighten U.S. physicians’ awareness of anthrax’s symptoms and treatments, according to Dr. Jason K. Blackburn.

“[Anthrax] is something that our international partners deal with on an annual basis [as] we can see the disease reemerging, or at least increasing, in annual reports on humans in a number of countries,” said Dr. Blackburn of the University of Florida in Gainesville, at a meeting on biodefense and emerging diseases sponsored by the American Society for Microbiology.

“Here in the United States, we’re seeing it shift

from a livestock disease [to] a wildlife disease, where we have these populations that we can’t reach with vaccines, and where surveillance is very logistically challenging,” he said.

Environmental factors can drive higher incidences of anthrax cases. Temperature, precipitation, and vegetation indices are key variables that facilitate anthrax transmission and spread of the disease. Geographically, lowland areas also have higher prevalences of the disease.

Dr. Blackburn and his colleagues used predictive models to quantify the theory that anthrax case rates increase during years that have wet springs followed by hot, dry summers in the region of Western Texas. Using these data would allow scientists and health care providers to predict which years would have an increased risk for anthrax cases in humans, Dr. Black-

burn said, and could help hospitals and clinics effectively prepare to treat a higher influx of these cases and prevent possible outbreaks.

Although relatively large numbers of human anthrax cases persist in parts of the world, cases in the United States have been mostly relegated to livestock.

However, during the last decade, there has been a noticeable shift in cases from livestock to wildlife. The newfound prevalence in wildlife species, along with the continued presence in domestic animals such as cattle and sheep, mean that transmission to humans could become even easier.

“Human cases are usually driven by direct human interaction with mammalian hosts,” said Dr. Blackburn. Dr. Blackburn did not report any disclosures.

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Lung cancer screening criteria may need changes

BY NICOLA GARRETT
Frontline Medical News

Fewer patients diagnosed with lung cancer are meeting the U.S. Preventive Services Task Force criteria for screening with low-dose computed tomography.

Screening criteria may need to be changed, since fewer American adults now have a smoking history of 30 pack-years and have quit within the last 15 years, according to Dr. Ping Yang of the division of epidemiology at the Mayo Clinic, Rochester, Minn., and her colleagues.

A retrospective analysis of patients with pathologically confirmed lung cancer in Olmsted County, Minn., between 1984 and 2011 found that, in 1984-1990, 57% of patients with diagnosed lung cancer met USPSTF screening guidelines. By 2005-2011, the figure had dropped significantly to 43%.

The proportion of women who would have been eligible under the criteria decreased from 52% to 37% in the same time period; the proportion of

men had dropped from 60% to 50%, they found.

“More sensitive screening criteria may need to be identified while balancing the potential harm from computed tomography,” Dr. Yang and her colleagues wrote (*JAMA* 2015; 313:853-5).

Lung cancer incidence trends in this study were

comparable with Surveillance, Epidemiology, and End Results data, but may not be generalizable to the U.S. population, they added.

The study was funded by the National Institutes of Health and the Mayo Clinic Foundation. The authors reported no relevant conflicts of interest.

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments:

Since 2005, a significant proportion of patients who are diagnosed with lung cancer were ineligible for low-dose CT screening for lung cancer under the current guidelines. This was most prevalent in the female population. The changing demographics of tobacco use in this country may be in part to blame. The proportion of patients currently smoking with a 30-plus-year smoking history or having quit within the last 15 years is declining. The cur-



rent criteria are excluding a significant number of patients who are eventually diagnosed with lung cancer. Maybe it's time to revisit the current guidelines – determine what variables are unique to this group of patients, evaluate those variables for increasing sensitivity of the screening guidelines, and update our current practice. For a screening program to work, we need to find more patients early, not less, while limiting the potential for harm from radiation exposure.

Periop atrial natriuretic peptide linked to lower recurrence

BY JENNIFER KELLY
SHEPPHARD
Frontline Medical News

Patients with lung cancer who underwent surgery to remove solid tumors and who were treated with atrial natriuretic peptide had significantly lower cancer recurrence than did untreated patients, a study showed.

Investigators retrospectively evaluated patients with lung cancer who underwent surgical removal of tumors; 77 patients received perioperative treatment with atrial natriuretic peptide (ANP), and 390 patients did not receive ANP treatment.

ANP-treated patients had signifi-

cantly greater 2-year relapse-free survival (RFS) after surgery than did those who did not receive ANP (91% vs. 75%, $P = .018$).

An analysis of propensity-matched patients also showed significantly greater 2-year RFS in the ANP group (91% vs. 67%, $P = .0013$), reported Dr. Takashi Nojiri of Osaka (Japan) University, and associates.

“We demonstrated that cancer recurrence after curative surgery was significantly lower in ANP-treated patients than in control patients, suggesting that ANP could potentially be used to prevent cancer recurrence after surgery,” wrote Dr. Nojiri and colleagues (*Proc. Natl. Acad. Sci. USA* 2015 March 16 [doi:10.1073/pnas.1417273112]).

ceived the ANP infusions versus those who did not (91% vs. 75%). Physiologically, ANP decreases the inflammatory response of the vascular endothelium to surgical stress. The decreased ability of tumor cells to adhere to the vascular endothelial cells decreases the chance of future metastasis. A large randomized multicenter trial should be undertaken before adopting this into practice, but the results are encouraging.

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: The same authors have previously published data in patients with elevated preoperative brain natriuretic peptide levels showing a decrease in cardiopulmonary complications after lung cancer surgery with perioperative atrial natriuretic peptide infusions. Looking retrospectively at the same group of patients, they found a significant 2-year relapse-free survival in those patients who re-

Nivolumab approved for advanced squamous NSCLC

BY LAURA NIKOLAIDES
Frontline Medical News

The Food and Drug Administration has expanded approval of the PD-1 inhibitor nivolumab to include treatment of patients who have metastatic squamous non-small cell lung cancer and progress following platinum-based chemotherapy.

The FDA approved nivolumab to treat patients who have metastatic melanoma and no longer respond to other drugs. Nivolumab for squamous non-small cell lung cancer (NSCLC) was reviewed under the FDA's priority review program, and was approved more than 3 months ahead of schedule, the FDA said.

Efficacy was established in a trial of 272 patients with metastatic squamous NSCLC; the median overall survival was increased by 3.2 months in 135 patients who received nivolumab, compared with 137 on docetaxel.

The safety and efficacy of nivolumab to treat squamous NSCLC was also supported by a single-arm trial of 117 participants who had progressed after receiving a platinum-based therapy and at least one additional systemic regimen. The objective response rate was 15%.

The most common side effects of nivolumab are fatigue, shortness of breath, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. The most serious side

VIEW ON THE NEWS

Dr. Jennifer D. Cox, FCCP, comments: New therapies for the treatment of advanced lung cancer are desperately needed. Nivolumab was recently approved for treatment of advanced lung cancer in patients that progressed on standard therapy. The early approval was done based on a 3.2-month survival over docetaxel. The common side effects would appear to be more inconvenient than detrimental. However, having seen and taken care of the patients with the severe immune-mediated side effects, I can say nivolumab is not a benign drug. My take on a medication that has any survival advantage will always be, ‘Is the quality of life for the patient during those 3 months good or is it poor?’ Survival is more than just the number of days a patient is alive, and I would like that kind of information provided as well.

effects are severe immune-mediated side effects involving healthy organs, including the lung, colon, liver, kidneys, and hormone-producing glands. The drug is marketed as Opdivo by Bristol-Myers Squibb.

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What if your PAH patient may not have PAH?



A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.¹

If you know what to look for, a V/Q scan makes it relatively easy to spot.¹



As many as **1 out of every 25** of your previously treated PE patients (>3 months of anticoagulation²) may develop CTEPH.^{3,4*}

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*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

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Screening for CTEPH in Patients With Suspected Pulmonary Hypertension



presented by

RICHARD CHANNICK, MD

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CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH¹:

- 1: Pulmonary arterial hypertension
- 2: PH due to left heart disease
- 3: PH due to lung diseases and/or hypoxia
- 4: **CTEPH**
- 5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term “post-pulmonary embolism syndrome” to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity.² The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH.^{2,3} As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.⁴

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.⁵

Symptoms of CTEPH are nonspecific⁶ and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema.⁷ Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.⁷

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH.⁸⁻¹⁰ It is this potential to effect a curative

treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries.¹¹ The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH.¹² Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR).¹¹ Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH.¹³ If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.¹³

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event.^{3,13} A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH.¹⁴ Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.¹⁵

The absence of prior acute PE does not exclude a diagnosis of CTEPH^{9,16,17}

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE.^{9,16,17} The true incidence of CTEPH may, therefore, be underestimated, because postembolism



As many as 1 in 25 survivors of acute PE (>3 months of anticoagulation) may go on to develop CTEPH within 2 years⁴

observational studies do not include patients who have no history of venous thromboembolism.¹³

HOW DO WE SCREEN FOR CTEPH?

As noted, symptoms of CTEPH are nonspecific, and as a result, CTEPH is often misdiagnosed and is under recognized in practice.⁶ If after at least 3 months of anticoagulation following an episode of acute PE a patient still has or develops symptoms of dyspnea, fatigue, decreased exercise capacity, or another of the symptoms of PH, one should suspect and either screen for CTEPH or refer the patient to a PH specialist who can perform CTEPH screening.^{18,19}

As noted above, as many as 30% of patients who are ultimately diagnosed with CTEPH may have no history of overt acute PE, so any patient who has unexplained dyspnea should also be screened for CTEPH.^{9, 16,17}

If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening¹⁷

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out.¹⁹ Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH.⁸ Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.⁸ Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH.²⁰ Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied.²⁰ Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.^{5,8,21-23} Though it can detect chronic thromboembolic disease in segmental, lobar, or main pulmonary arteries, CTPA may miss disease that is

confined to very distal segmental or subsegmental pulmonary arteries.^{8,24}

The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.⁸ It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. V/Q scanning also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings.

PTE surgery is the first-line treatment of choice for surgical candidates who have CTEPH¹⁵

Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.²⁵ This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that “underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH.”⁷⁸ Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.^{6,26} If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

CONFIRMATION OF CTEPH DIAGNOSIS

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥ 25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.⁸ CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.^{5,8}

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient’s surgery. Operability assessment must consider the patient’s risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.⁸ If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.⁸ This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well

be deemed operable by another experienced CTEPH team.

CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOENDARTERECTOMY

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.⁵ Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.⁸⁻¹⁰ Rather than reserving PTE surgery as a “last-ditch” treatment option, patients who have operable CTEPH should be referred for surgery without delay.⁸ Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,⁸ anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.⁷ About two-thirds of patients have normal hemodynamics following PTE.²⁷

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*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).⁴

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ICD-10 cometh

BY DR. MICHAEL E. NELSON, FCCP

Just when you thought the flu season was over... The ICD-10 version!
For our second set of codes we have chosen influenza as this is a diagnosis fresh on the mind

of most physicians at this time. This set of codes is quite complex and also contains “placeholders.” According to the ICD-10-CM Official Guidelines for Coding and Reporting available at www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html,

The ICD-10-CM utilizes a placeholder character “X.” The X is used as a placeholder at certain codes to allow for future expansion.

Where a placeholder exists, the X must be used in order for the code to be considered a valid code. The ICD-10 CM codes for influenza are listed below.

Influenza and pneumonia (J09-J18)

Excludes 2:

allergic or eosinophilic pneumonia (J82)
aspiration pneumonia NOS (J69.0)
meconium pneumonia (P24.01)
neonatal aspiration pneumonia (P24.-)
pneumonia due to solids and liquids (J69.-)
congenital pneumonia (P23.9)
lipid pneumonia (J69.1)
rheumatic pneumonia (I00)
ventilator associated pneumonia (J95.851)

J09 Influenza due to identified novel influenza A virus with pneumonia

Excludes 1:

influenza due to other identified influenza virus (J10.-)
influenza due to unidentified influenza virus (J11.-)
seasonal influenza due to other identified influenza virus (J10.-)
seasonal influenza due to unidentified influenza virus (J11.-)

J09.X1 Inclusion Terms:

Avian influenza
Bird influenza
Influenza A/H5N1
Influenza of other animal origin, not bird or swine
Swine influenza virus (viruses that normally cause infections in pigs)

J09.X1 Influenza due to identified novel influenza A virus with pneumonia

Code Also: , if applicable, for associated:
lung abscess (J85.1)
other specified type of pneumonia

J09.X2 Influenza due to identified novel influenza A virus with other respiratory manifestations

Inclusion Terms:

Influenza due to identified novel influenza A virus NOS
Influenza due to identified novel influenza A virus with laryngitis
Influenza due to identified novel influenza A virus with pharyngitis
Influenza due to identified novel influenza A virus with upper respiratory symptoms

Use Additional:

code, if applicable, for associated:
pleural effusion (J91.8)
sinusitis (J01.-)

J09.X3 Influenza due to identified novel influenza A virus with gastrointestinal manifestations

Inclusion Terms:

Influenza due to identified novel influenza A virus gastroenteritis

Excludes 1:

‘intestinal flu’ [viral gastroenteritis] (A08.-)

J09.X9 Influenza due to identified novel influenza A virus with other manifestations

Inclusion Terms:

Influenza due to identified novel influenza A virus with encephalopathy
Influenza due to identified novel influenza A virus with myocarditis
Influenza due to identified novel influenza A virus with otitis media

Use Additional:

code to identify manifestation

J10 Influenza due to other identified influenza virus

Excludes 1:

influenza due to avian influenza virus (J09.X-)
influenza due to swine flu (J09.X-)
influenza due to unidentified influenza virus (J11.-)

J10.0 Code Also: associated lung abscess, if applicable (J85.1)

J10.00 Influenza due to other identified influenza virus with unspecified type of pneumonia

J10.01 Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia

J10.08 Influenza due to other identified influenza virus with other specified pneumonia

J10.1 Influenza due to other identified influenza virus with other respiratory manifestations

Inclusion Terms:

Influenza due to other identified influenza virus NOS
Influenza due to other identified influenza virus with laryngitis
Influenza due to other identified influenza virus with pharyngitis
Influenza due to other identified influenza virus with upper respiratory symptoms

Use Additional:

code for associated pleural effusion, if applicable (J91.8)
code for associated sinusitis, if applicable (J01.-)

J10.2 Influenza due to other identified influenza virus with gastrointestinal manifestations

Inclusion Terms:

Influenza due to other identified influenza virus gastroenteritis

Excludes 1:

intestinal flu’ [viral gastroenteritis] (A08.-)

J10.8 Influenza due to other identified influenza virus with other manifestations

J10.81 Influenza due to other identified influenza virus with encephalopathy

J10.82 Influenza due to other identified influenza virus with myocarditis

J10.83 Influenza due to other identified influenza virus with otitis

Use Additional: code for any associated perforated tympanic membrane (H72.-)

J10.89 Influenza due to other identified influenza virus with other manifestations

Use Additional:

codes to identify the manifestations

J11 Influenza due to unidentified influenza virus

J11.0 Influenza due to unidentified influenza virus with

Code Also: associated lung abscess, if applicable (J85.1)

J11.00 Influenza due to unidentified influenza virus with unspecified type of pneumonia

Inclusion Terms:

Influenza with pneumonia NOS

J11.08 Influenza due to unidentified influenza virus with specified pneumonia

Code Also: other specified type of pneumonia

J11.1 Influenza due to unidentified influenza virus with other respiratory manifestations

Inclusion Terms:

Influenza NOS
Influenza laryngitis NOS
Influenza pharyngitis NOS
Influenza with upper respiratory symptoms NOS

Use Additional:

code for associated pleural effusion, if applicable (J91.8)
code for associated sinusitis, if applicable (J01.-)

J11.2 Influenza due to unidentified influenza virus with gastrointestinal manifestations

Inclusion Terms:

Influenza gastroenteritis NOS

Excludes 1:

‘intestinal flu’ [viral gastroenteritis] (A08.-)

J11.8 Influenza due to unidentified influenza virus with other manifestations

J11.81 Influenza due to unidentified influenza virus with encephalopathy

Inclusion Terms:

Influenza encephalopathy NOS

J11.82 Influenza due to unidentified influenza virus with myocarditis

Inclusion Terms:

Influenza myocarditis NOS

J11.83 Influenza due to unidentified influenza virus with otitis media

Inclusion Terms:

Influenza otitis media NOS

Use Additional:

code for any associated perforated tympanic membrane (H72.-)

J11.89 Influenza due to unidentified influenza virus with other manifestations

Use Additional:

codes to identify the manifestations

J12 Viral pneumonia, not elsewhere classified

Code First:

associated influenza, if applicable (J09.X1, J10.0-, J11.0-)

Code Also:

associated abscess, if applicable (J85.1)

Includes:

bronchopneumonia due to viruses other than influenza viruses
aspiration pneumonia due to anesthesia during labor and delivery (074.0)

Excludes 1:

aspiration pneumonia due to anesthesia during pregnancy (029)
aspiration pneumonia due to anesthesia during puerperium (089.0)
aspiration pneumonia due to solids and liquids (J69.-)
aspiration pneumonia NOS (J69.0)
congenital pneumonia (P23.0)
congenital rubella pneumonitis (P35.0)
interstitial pneumonia NOS (J84.9)
lipid pneumonia (J69.1)
neonatal aspiration pneumonia (P24.-)

J12.0 Adenoviral pneumonia

J12.1 Respiratory syncytial virus pneumonia

J12.2 Parainfluenza virus pneumonia

J12.3 Human metapneumovirus pneumonia

J12.8 Other viral pneumonia

12.81 Pneumonia due to SARS-associated coronavirus

Inclusion Terms:

Severe acute respiratory syndrome NOS

12.89 Other viral pneumonia

12.9 Viral pneumonia, unspecified

California physicians sue state over suicide law

BY ALICIA GALLEGOS
Frontline Medical News

A group of physicians and patients are suing the state of California over a law that they say exposes doctors to criminal prosecution for providing terminally ill patients aid in dying.

Three doctors and three cancer patients – two of whom are also doctors – filed suit against the state, calling on California to clarify a portion of its assisted-suicide statute. The law makes it a felony to deliberately help a person commit suicide.

In their suit, the plaintiffs claim physicians who write prescriptions for mentally competent, terminally ill patients should not face legal penalties. The choice for a peaceful death by a dying patient is not suicide, nor is a physician assisting such a patient in “committing suicide,” the complaint argues. In addition, the physicians assert that patients facing the end of their lives have a right under the California state Constitution to make autonomous decisions about their bodies and how they will die.

In a statement, plaintiff Dr. Robert Brody, professor of medicine at the University of California, San Francisco, said competent, terminally ill adults have the right to a peaceful death in a controlled and clinically sound way.

“The current murky legal landscape means that physicians are placed at risk and must choose between potentially skirting the law to respect their patients’ choices or abandoning them to bad information, uncertainty, or violence,” he said in the statement.

The lawsuit comes after the

high-profile death of terminally ill patient Brittany Maynard, who moved from California to Oregon to take advantage of that state’s Death With Dignity law.

The Disability Rights Legal Center,

which is representing the plaintiffs in the California case, also recently filed suit in New York over the same issue. In that case, several physicians and patients are asking New York judges to clarify the ability of mentally

competent, terminally ill New York patients to obtain aid in dying from their physician.

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*When you need to
increase bronchodilation for
your patients with COPD...*



Watchman device alternative to warfarin in AF

BY ELIZABETH MEHCATIE
Frontline Medical News

The Watchman left atrial appendage closure device has been approved in the United States as

an alternative to warfarin for patients with nonvalvular atrial fibrillation, for a narrower indication than the one submitted for approval to the Food and Drug Administration.

The device is a percutaneously deliv-

ered permanent cardiac implant placed in the left atrial appendage (LAA) to prevent the embolization of thrombi formed there, and is manufactured by Boston Scientific. The FDA approved the Watchman for reducing the risk

of thromboembolism from the LAA in patients with nonvalvular atrial fibrillation “who are at increased risk for stroke and systemic embolism based on CHADS₂ or CHA₂DS₂-VASc scores; are deemed by their physicians

Indication

Striverdi® Respimat® (olodaterol) Inhalation Spray is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations: STRIVERDI RESPIMAT 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 (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life threatening condition, or used as rescue therapy for acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting beta₂ agonist.

STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂ agonists as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted.

NEW

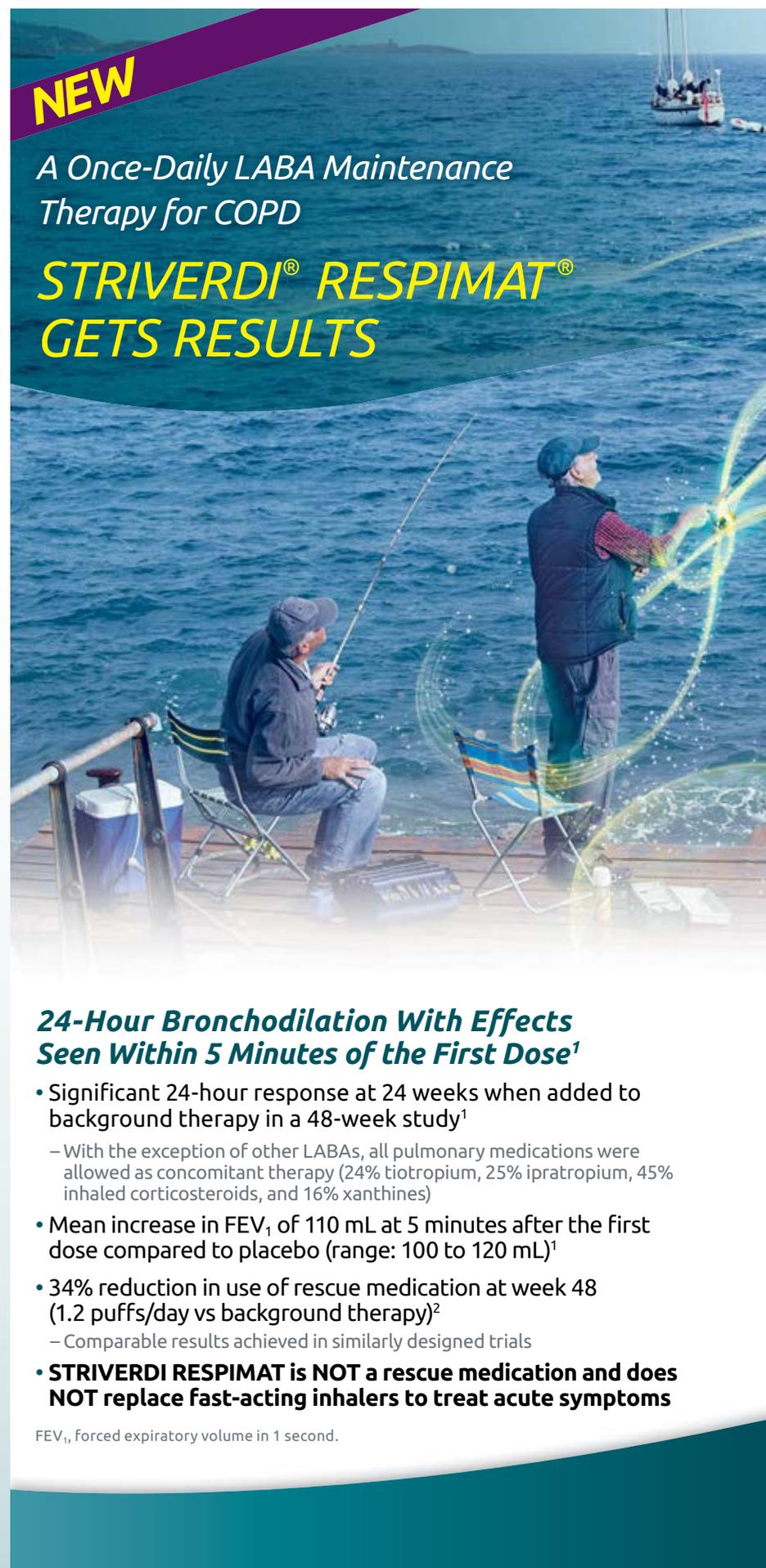
A Once-Daily LABA Maintenance Therapy for COPD

STRIVERDI® RESPIMAT® GETS RESULTS

24-Hour Bronchodilation With Effects Seen Within 5 Minutes of the First Dose¹

- Significant 24-hour response at 24 weeks when added to background therapy in a 48-week study¹
 - With the exception of other LABAs, all pulmonary medications were allowed as concomitant therapy (24% tiotropium, 25% ipratropium, 45% inhaled corticosteroids, and 16% xanthines)
- Mean increase in FEV₁ of 110 mL at 5 minutes after the first dose compared to placebo (range: 100 to 120 mL)¹
- 34% reduction in use of rescue medication at week 48 (1.2 puffs/day vs background therapy)²
 - Comparable results achieved in similarly designed trials
- **STRIVERDI RESPIMAT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms**

FEV₁, forced expiratory volume in 1 second.



to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device, compared to warfarin," according to a statement issued by the company.

The approved indication is worded differently from the proposed indica-



COURTESY BOSTON SCIENTIFIC

tion submitted to the FDA for approval and discussed at an FDA panel meeting, to "prevent thromboembolism from the left atrial appendage." The changes include the replacement of "prevent" with "reduce the risk" of thromboembolism, and the addition of the following qualifiers: In patients who "are deemed by their physicians to be suitable for warfarin," and who have "an

appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin."

At a meeting of the FDA's Circulatory System Devices Panel, the panel voted 6-5 with 1 abstention that the benefits of the device outweighed its risks for the proposed indication.

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To learn more about
STRIVERDI RESPIMAT,
visit www.STRIVERDI.com

Please see Brief Summary of full Prescribing Information, including **boxed WARNING** for STRIVERDI RESPIMAT on adjacent page.

STRIVERDI RESPIMAT can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms, and should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. If cardiovascular symptoms occur, STRIVERDI RESPIMAT may need to be discontinued.

STRIVERDI RESPIMAT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Be alert to hypokalemia and hyperglycemia.

Immediate hypersensitivity reactions, including angioedema, may occur. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

The most commonly reported adverse reactions ($\geq 2\%$ incidence and more than placebo) with STRIVERDI RESPIMAT (and placebo) were nasopharyngitis, 11.3% (7.7%); upper respiratory tract infection, 8.2% (7.5%); bronchitis, 4.7% (3.6%); urinary tract infection, 2.5% (1.0%); cough, 4.2% (4.0%); dizziness, 2.3% (2.1%); rash, 2.2% (1.1%); diarrhea, 2.9% (2.5%); back pain, 3.5% (2.7%); and arthralgia 2.1% (0.8%).

STRIVERDI RESPIMAT should be used with extreme caution in patients 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.

STRIVERDI RESPIMAT should be used with caution in patients treated with additional adrenergic drugs, non-potassium-sparing diuretics, and beta-blockers.

STRIVERDI RESPIMAT is for oral inhalation only.

Please see full Prescribing Information, including **boxed WARNING**, Medication Guide, and Instructions for Use.

References:

1. STRIVERDI RESPIMAT prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.
2. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

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STRIVERDI[®]
RESPIMAT[®]
(olodaterol)
INHALATION SPRAY



Long-term DAPT offers ongoing post-MI benefit

BY MITCHEL L. ZOLER
Frontline Medical News

SAN DIEGO – The idea that patients with established coronary disease can derive important, secondary-prevention

benefit from prolonged dual-antiplatelet therapy received a major boost with the results of a major, international controlled trial with more than 21,000 patients.

Results from the PEGASUS-TIMI

54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) showed putting

post-myocardial infarction patients on dual-antiplatelet therapy (DAPT) with aspirin and the thienopyridine ticagrelor (Brilinta) for a median of 33 months cut the combined incidence of cardiovascular death, MI, or stroke by a relative 15%, compared with patients on aspirin alone as well as the other standard treatments used for post-MI patients, Dr. Marc S. Sabatine reported at the annual meeting of the American College of Cardiology.

The findings added to the growing body of evidence that long-term – and possibly lifelong – DAPT is a key part of secondary prevention. Last year, results from the DAPT (Dual Antiplatelet Therapy) trial (N. Engl. J. Med. 2014;371:2155-66) supplied evi-



Dr. Robert Harrington: Assessing a patient's bleeding risk is important.

dence for this in acute coronary syndrome patients who had undergone percutaneous coronary intervention. The PEGASUS-TIMI 54 trial did not require that enrolled post-MI patients had undergone PCI, but the reality is that this is the way most MI patients get managed, and in PEGASUS-TIMI 54 roughly 83% of the patients had a PCI history.

The new findings also highlighted the risk-benefit trade-off that DAPT means for patients. In PEGASUS-TIMI 54 the increased incidence of major bleeding events roughly matched the decreased rate of major cardiovascular events prevented. But while the incidence of bleeds categorized as TIMI major bleeds more than doubled in the patients randomized to DAPT, compared with those on aspirin only, the prolonged treatment with ticagrelor did not result in an increase in fatal bleeds or in intracranial hemorrhages, the two most feared types of TIMI major bleeds.

“I’d much rather prevent cardiovascular deaths, MIs, and strokes even at the expense of causing reversible, nonfatal bleeding events,” said Dr. Sabatine, professor of medicine at Har-

Continued on following page

STRIVERDI® RESPIMAT® (olodaterol) Inhalation Spray FOR ORAL INHALATION
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications, Warnings and Precautions].

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STRIVERDI RESPIMAT is a long-acting beta₂-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. **Important Limitations of Use:** STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STRIVERDI RESPIMAT in asthma have not been established.

CONTRAINDICATIONS: All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions]. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

WARNINGS AND PRECAUTIONS: Asthma-Related Death [see Boxed Warning]: Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists 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 long-acting beta₂-adrenergic agonists. A 28-week, placebo-controlled US study comparing the safety of another long-acting beta₂-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta₂-adrenergic agonists, including STRIVERDI RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STRIVERDI RESPIMAT has been conducted. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Contraindications]. **Deterioration of Disease and Acute Episodes:** STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STRIVERDI RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STRIVERDI RESPIMAT in this setting is inappropriate. STRIVERDI RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STRIVERDI RESPIMAT 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 STRIVERDI RESPIMAT, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four 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 STRIVERDI RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how to use it. 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 STRIVERDI RESPIMAT no longer controls symptoms of bronchoconstriction, or 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 dosage of STRIVERDI RESPIMAT beyond the recommended dose is not appropriate in this situation. **Excessive Use of STRIVERDI RESPIMAT and Use with Long-Acting Beta₂-Agonists:** As with other inhaled drugs containing beta₂-adrenergic agonists, STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. **Paradoxical Bronchospasm:** As with other inhaled beta₂-agonists, STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted. **Cardiovascular Effects:** STRIVERDI RESPIMAT, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STRIVERDI RESPIMAT may need to be discontinued. In addition, beta₂-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Long acting beta₂-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. **Co-existing Conditions:** STRIVERDI RESPIMAT, like other sympathomimetic amines, should be used with caution in patients

with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia: Beta-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 [see Drug Interactions], which may increase the susceptibility for cardiac arrhythmias. Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of STRIVERDI RESPIMAT with the rates similar to those for placebo controls. STRIVERDI RESPIMAT has not been investigated in patients whose diabetes mellitus is not well controlled. **Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including angioedema, may occur after administration of STRIVERDI RESPIMAT. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

ADVERSE REACTIONS: Long-acting beta₂-adrenergic agonists, such as STRIVERDI RESPIMAT, increase the risk of asthma-related death. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [see Boxed Warning and Warnings and Precautions]. Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The STRIVERDI RESPIMAT clinical development program included seven dose-ranging trials and eight confirmatory trials. Four of the confirmatory trials were 6-week cross-over trials and four were 48-week parallel group trials. Adverse reactions observed in the dose-ranging trials and four 6-week cross-over trials were consistent with those observed in the 48-week parallel group trials, which formed the primary safety database. The primary safety database consisted of pooled data from the four 48-week double-blind, active and placebo-controlled, parallel group confirmatory clinical trials. These trials included 3104 adult COPD patients (77% males and 23% females) 40 years of age and older. Of these patients, 876 and 883 patients were treated with STRIVERDI RESPIMAT 5 mcg and 10 mcg once-daily, respectively. The STRIVERDI RESPIMAT groups were composed of mostly Caucasians (66%) with a mean age of 64 years and a mean percent predicted FEV₁ at baseline of 44% for both the 5 mcg and 10 mcg treatment groups. Control arms for comparison included placebo in all four trials plus formoterol 12 mcg in two trials. In these four clinical trials, seventy-two percent (72%) of patients exposed to any dose of STRIVERDI RESPIMAT reported an adverse reaction compared to 71% in the placebo group. The proportion of patients who discontinued due to an adverse reaction was 7.2% for STRIVERDI RESPIMAT treated patients compared to 8.8% for placebo treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation, pneumonia, and atrial fibrillation. Table 1 shows all adverse drug reactions reported by at least 2% of patients (and higher than placebo) who received STRIVERDI RESPIMAT 5 mcg during the 48-week trials.

Table 1: Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to STRIVERDI RESPIMAT 5 mcg: Pooled data from the four 48-week, double-blind, active- and placebo-controlled clinical trials in COPD patients 40 years of age and older

Treatment	STRIVERDI 5 mcg once-daily	Placebo
Body system (adverse drug reaction)	n=876 n (%)	n=885 n (%)
Infections and infestations		
Nasopharyngitis	99 (11.3)	68 (7.7)
Upper Respiratory Tract Infection	72 (8.2)	66 (7.5)
Bronchitis	41 (4.7)	32 (3.6)
Urinary Tract Infection	22 (2.5)	9 (1.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	37 (4.2)	35 (4.0)
Nervous system disorders		
Dizziness	20 (2.3)	19 (2.1)
Skin and subcutaneous tissue disorders		
Rash*	19 (2.2)	10 (1.1)
Gastrointestinal disorders		
Diarrhea	25 (2.9)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back Pain	31 (3.5)	24 (2.7)
Arthralgia	18 (2.1)	7 (0.8)

* Rash includes a grouping of similar terms.

Additional adverse reactions that occurred in greater than 2% (and higher than placebo) of patients exposed to STRIVERDI RESPIMAT 10 mcg were pneumonia, constipation, and pyrexia. Lung cancers were reported in 6 (0.7%), 3 (0.3%), and 2 (0.2%) patients who received STRIVERDI RESPIMAT 10 mcg, 5 mcg, and placebo, respectively.

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 STRIVERDI RESPIMAT may be potentiated [see Warnings and Precautions]. **Xanthine Derivatives, Steroids, or Diuretics:** Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of STRIVERDI RESPIMAT [see Warnings and Precautions].

Non-Potassium Sparing Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs:** STRIVERDI RESPIMAT, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and STRIVERDI RESPIMAT 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. **Inhibitors of Cytochrome P450 and P-gp Efflux Transporter:** In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of maximum plasma concentrations and AUC was observed. STRIVERDI RESPIMAT was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies with STRIVERDI RESPIMAT in pregnant women. STRIVERDI RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. STRIVERDI RESPIMAT was not teratogenic in rats at inhalation doses approximately 2,731 times the maximum recommended human daily inhalation dose (MRHDID) on an AUC basis (at a rat maternal inhalation dose of 1,054 mcg/kg/day). Placental transfer of STRIVERDI RESPIMAT was observed in pregnant rats. STRIVERDI RESPIMAT has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7,130 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 2,489 mcg/kg/day). STRIVERDI RESPIMAT exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at an inhalation dose approximately 1,353 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 974 mcg/kg/day).

Labor and Delivery: There are no adequate and well-controlled human studies that have investigated the effects of STRIVERDI RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STRIVERDI RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. **Nursing Mothers:** Olodaterol, the active component of STRIVERDI RESPIMAT, and/or its metabolites are excreted into the milk of lactating rats. Excretion of olodaterol and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of STRIVERDI RESPIMAT on nursing infants. Caution should be exercised when STRIVERDI RESPIMAT is administered to nursing women. **Pediatric Use:** STRIVERDI RESPIMAT is not indicated for use in children. The safety and effectiveness of STRIVERDI RESPIMAT in the pediatric population have not been established. **Geriatric Use:** Based on available data, no adjustment of STRIVERDI RESPIMAT dosage in geriatric patients is necessary. Of the 876 patients who received STRIVERDI RESPIMAT at the recommended dose of 5 mcg once-daily in the clinical studies from the pooled 1-year database, 485 were less than or equal to 65 years of age and 391 (44.6%) were greater than 65 years of age. No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Hepatic Impairment:** Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed. **Renal Impairment:** Subjects with severe renal impairment showed no clinically relevant changes in C_{max} or AUC compared to their healthy controls.

OVERDOSAGE: The expected signs and symptoms with overdose of STRIVERDI RESPIMAT are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of STRIVERDI RESPIMAT. Treatment of overdose consists of discontinuation of STRIVERDI RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdose of STRIVERDI RESPIMAT. Cardiac monitoring is recommended in cases of overdose.

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Continued from previous page

vard Medical School in Boston and chairman of the TIMI Study Group at Brigham and Women's Hospital.

Another notable adverse effect from ticagrelor treatment was a roughly threefold increased incidence of dyspnea, which led to drug discontinuation in 5%-7% of patients, depending on whether they received ticagrelor at 60 mg b.i.d. or 90 mg b.i.d. The study results showed a reduced rate of both bleeding and dyspnea in patients randomized to receive the 60-mg b.i.d. dosage, compared with those who received the 90-mg b.i.d. dosage, which is the standard ticagrelor dosage and the formulation now sold.

At the same time, the efficacy of the 60-mg b.i.d. dosage for preventing ischemic events equaled that of the higher dosage. But as of today, it is impossible for a physician to prescribe a 60-mg formulation of ticagrelor because the manufacturer does not sell it.

Several cardiologists from PEGASUS-TIMI 54 at the meeting said that they agreed with Dr. Sabatine and felt that the benefits from prolonged DAPT with ticagrelor outweighed the downside of an increased bleeding risk.

"I think that the benefit is greater than the risk. None of us wants to see patients experience bleeding, but I was encouraged that fatal bleeds and intracranial hemorrhages were no different," commented Dr. Elliott M. Antman, professor of medicine at Harvard.

"The benefits outweigh the bleeding risk, but I wouldn't trivialize the bleeding risk. Assessing a patient's bleeding risk is really important," commented Dr. Robert Harrington, professor of medicine at Stanford (Calif.) University.

But others at the meeting said that the elevated bleeding risk gave them pause. "There clearly is a price to be paid even if extended-duration DAPT reduces MI and stent thrombosis. I believe only the highest-risk patients – those with acute coronary syndrome and ST-elevation MI – are the ones for whom I'd even consider it. Unless we can reduce bleeding risk, maybe with even lower doses [of ticagrelor], stopping aspirin, or using a reversal agent, we will be causing bleeds that are very relevant to patients," commented Dr. Ajay J. Kirtane, an interventional cardiologist at Columbia University in New York.

Dr. Kirtane also questioned whether TIMI major bleeding was the appropriate measure of bleeding risk in the context of a study like PEGASUS-TIMI 54. "Historically, TIMI ma-

VIEW ON THE NEWS

Post-MI patients need long-term secondary prevention

The results from PEGASUS-TIMI 54 provide a powerful message for secondary prevention: Patients who have had a prior myocardial infarction remain at an increased risk for subsequent ischemic events, even when maintained on what is currently standard therapy and even when they are several years out from their event.

We have no perfect antiplatelet drugs. Treating patients like those enrolled in the trial with an agent like ticagrelor further reduced their risk for ischemic events, but at the price of increasing their risk for major bleeds. The good news was that the rates of fatal bleeds and intracranial hemorrhages did not increase with ticagrelor treatment. Selecting the right patients to treat with prolonged dual-antiplatelet therapy (DAPT) requires good judgment as well as understanding the patient's values and preferences. From the clinician's perspective, it is the fatal bleeds or intracranial hemorrhages that are most comparable to cardiovascular deaths, myocardial infarctions, or strokes. Although I do not want to minimize the impact of other major or minor bleeds that might require transfusions, these are not considered as important for patient well-being as the ischemic events that ticagrelor treatment reduced.



I believe that the findings from PEGASUS-TIMI 54 will work their way into everyday practice with clinicians increasingly keeping patients on prolonged DAPT following percutaneous coronary interventions or a myocardial infarction. Problems with bleeding or dyspnea usually appear relatively early for patients on DAPT. The new findings give us increased confidence that once these patients get to a year out from the onset of treatment, they can safely continue treatment and derive ongoing benefit from it, especially higher-risk patients, even though the 60-mg formulation of ticagrelor is not currently available. The new results complement those reported last year from the DAPT trial, which also addressed the safety and incremental value of more prolonged DAPT for higher-risk MI and acute coronary syndrome patients.

Dr. Richard C. Becker is professor and director of the University of Cincinnati Heart, Lung, and Vascular Institute. He has been a consultant to and received research grants from AstraZeneca, the company that sponsored PEGASUS-TIMI 54 and that markets ticagrelor (Brilinta). He made these comments in an interview.

major bleeding was derived from studies of acute heart attack patients getting fibrinolytic therapy.

"That is a very different population from this one. In my mind, the combination of TIMI major and minor bleeding would be more encompassing, and for patients the bleeding risks of these therapies are real and have been associated with bad sequelae," he said in an interview.



Dr. Elliott M. Antman: I think the benefit is greater than the risk.

When placed in the context of prior reports, the new findings also raise the possibility that the generic, and hence much cheaper, thienopyridine clopidogrel might provide roughly the same long-term benefit as the more expensive ticagrelor, especially for patients without a genetic profile that makes them poor clopidogrel metabolizers. This may be an attractive option for patients who have a problem paying for ticagrelor long term. "I'd

rather prescribe a patient a cheaper medication that might be a bit less effective than create an economic hardship," Dr. Harrington said in an interview. The results from the DAPT trial, which included some post-PCI patients who received long-term DAPT with clopidogrel plus aspirin, "give you a certain comfort" with the idea of substituting clopidogrel for ticagrelor when



Dr. Marc S. Sabatine: DAPT cut the incidence of CV death, MI, or stroke.

affordability is a major concern, Dr. Harrington noted.

PEGASUS-TIMI 54 enrolled 21,162 patients who were 1-3 years out from a prior myocardial infarction at 1,161 sites in 31 countries. Enrolled patients also had to be at least 50 years old, and have at least one additional risk factor for ischemic events such as age 65 years or older, diabetes, multivessel coronary artery disease, or chronic renal dysfunction. The enrolled patients averaged 1.7 years out from their index MI.

Randomization assigned patients to treatment with 90 mg ticagrelor b.i.d., 60 mg ticagrelor b.i.d., or placebo, and all patients also received daily treatment with 75-150 mg aspirin.

After a median follow-up of 33 months on treatment, the combined rate of cardiovascular death, myocardial infarction, or stroke – the study's primary endpoint – occurred in 7.85% of patients on the 90-mg ticagrelor dosage, 7.77% of those on the 60-mg dosage, and 9.04% of patients on placebo receiving aspirin only, statistically significant differences for the study's primary endpoint for each of the two ticagrelor dosages.

Concurrent with the report at the meeting, the results also appeared online (*N. Engl. J. Med.* 2015; [doi:10.1056/nejmoa1500857]). The findings translated into hazard ratios of 0.85 for the 90-mg dosage and 0.84 for the 60-mg dosage, compared with placebo.

The study's primary safety outcome was the incidence of TIMI major bleeding events, which occurred in 2.60% of patients on the higher ticagrelor dosage, 2.30% of those on the 60-mg dosage, and 1.06% of those on placebo, which converted into hazard ratios of 2.69 for the 90-mg dosage and 2.32 for the lower dosage for TIMI major bleeds, compared with aspirin alone.

FROM THE EVP/CEO: Solutions to make your tomorrows > today

BY PAUL A. MARKOWSKI, CAE

As a membership organization, CHEST is committed to supporting you and offering solutions that can make your tomorrows greater than today. It's incumbent on us to ensure you continually derive value from our organization, and that's the motive that led us to implement a robust, new association management software (AMS) system to improve and simplify the way you engage with us online. The AMS is scheduled to go live the first week of May, so I'd like to share what that will mean for you.

The main benefit you'll notice is single sign-on. Single sign-on is a feature that connects related, but independent, software systems, so a user can log in once and access all systems without needing to log in repeatedly for each individual system. Today, you're required to log in to each of our systems separately. Single sign-on will connect the systems for our store, Learning Site, CME claiming, event registration, hotel reservations, session submission, and conflict of interest disclosure. When you log in to any of these systems, you'll have

access to all of them without needing to log in again. You'll be able to move from one system to the next without interruption for signing in.



MR. MARKOWSKI

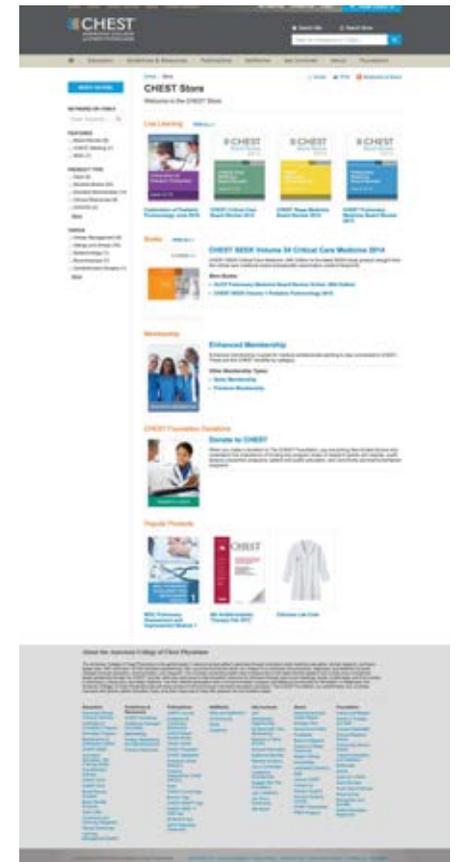
For the most part, you won't see many changes to chestnet.org after the AMS is live. The interface will remain very familiar—until you visit the store. Our online store has had a major facelift! You'll immediately notice cleaner, more attractive page designs and more intuitive navigation. And, new to the store is an easy way to renew your CHEST membership. If you have trouble finding what you're looking for, the upgraded search feature will allow you to filter results with further refinement. You'll be able to limit your search to the store only or continue to search across chestnet.org, the journal *CHEST*, and our meeting sites. It will be an improved experience, offering popular features similar to other retail sites.

The CHEST staff has been com-

mitted to implementing the AMS, working hard for many months. They've developed, designed, trained, tested, and debugged to deliver a better experience for you come May. Despite this skilled and careful work, it's realistic to expect there may be initial hiccoughs after the AMS goes live. If you experience any difficulty whatsoever, I encourage you to contact our Customer Support team at chestcustomersupport@chestnet.org, 800/343-2227, or 224/521-9800. They're top notch and will be ready to help you resolve your issues.

I'm looking forward to going live with the AMS in May. But, I don't think of that day as our finish line, marking the end of months of intense development. Rather, it's our starting line, marking the beginning of improved online solutions to enhance your engagement with us. And, since it's only the beginning, you can expect that we'll continue our work to help you achieve more through improved access to information and resources online. It's our way of offering solutions to help make your tomorrow greater than today.

Check out the new AMS features next month, and let me know what

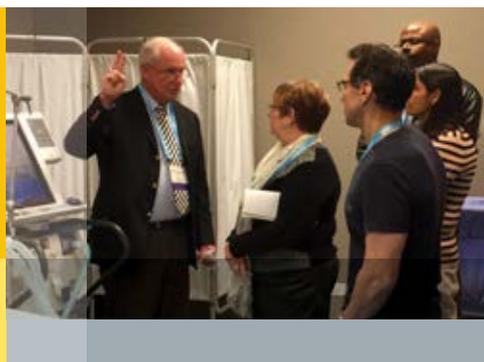


you think. And, as always, I invite you to follow me on Twitter (@PMarkowskiACCP), or look for me at upcoming CHEST events.

Mechanical Ventilation: Advanced Critical Care Management

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Acquire extensive knowledge in advanced techniques and skills for mechanical ventilation in the critically ill patient—including the latest advances in ventilator technology—through lectures; interactive discussion; hands-on, small group workshops; and case-based exercises.

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- Management of obstructive and parenchymal lung disease
- Management of hypoxemia in conventional management, HFOV/APRV and ECMO
- Interactive sessions on novel ventilator modes designed to optimize patient ventilator synchrony

Who Should Attend?

Pulmonary and critical care physicians and intensivists, pulmonary and critical care fellows, hospitalists, respiratory therapists, critical care nurses, nurse practitioners, and physician assistants are encouraged to attend.

> Register Now chestnet.org/live-learning

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CHEST membership is becoming more relevant to your practice than ever before.

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We're streamlining our online systems to make it easier for you to access the rich array of quality resources we offer.

> Learn More Today chestnet.org/tomorrow

Experience Montréal's past, be part of chest medicine's future

Montréal, Canada, will welcome the CHEST Annual Meeting 2015, October 24 – 28, and it couldn't be more appropriate.

Montréal will set a perfect backdrop of old world charm mixed with North American energy. CHEST will fit right in with over 8 decades of clinically relevant annual meetings and its exciting schedule of innovative, state-of-the-art educational opportunities. You may come for the education, but you won't want to leave without exploring this charming city.

Just minutes away from the Palais des congrès de Montréal, the convention center, Old Montréal offers a glimpse into Montréal's history blended with hip, urban hotspots. Complete with cobblestone paths, chic art galleries, 19th century architecture, and trendy boutiques, this neighborhood will keep you busy during your spare time.

Start planning your itinerary today with these recommended spots in Old Montréal:

- Visit Notre-Dame Basilica. This Gothic Revival style church was built between 1672 and 1683. Admire the dramatic architecture and colorful interior as you take a guided tour to learn about the history, architecture, and much more.
- Go shopping and dine at Marche Bonsecours. This historic building is home to galleries, boutiques, and restaurants. You'll recognize its imposing silver dome in this historic district.
- Explore the outdoors at The Quays of the Old Port, a park that runs alongside the St. Lawrence River. You'll find festivals and cultural events. Plus, there are walking paths, restaurants, and terraces with beautiful views of the city.
- Learn about local history at the Pointe-a-Cal-



Notre-Dame Basilica, Montréal

liere, Montréal Museum of Archaeology and History. This national historical and archaeological site leads visitors through centuries of history.

- Visit Chateau Ramezay, a private museum that details the history of Québec and Montréal.
- Dine at Olive & Gourmando. While there is regularly a line to get into this cafe, the cuisine is worth the wait. You'll enjoy creative sandwiches, local beer and wine selections, and pastries galore!

After you visit the past in Old Montréal's historic neighborhood, you'll find yourself recharged and ready for the latest in pulmonary, critical care, and sleep medicine education. CHEST 2015 will give you a glimpse into the future of chest medicine with the latest guidelines, abstracts, and simulation education. Find everything you need to know to make the best clinical decisions and inspire your patient care. Learn more at chestmeeting.chestnet.org.

New publisher chosen for CHEST

Elsevier, a world-leading provider of scientific, technical, and medical information products and services, and the American College of Chest Physicians (CHEST), a world-renowned publisher of evidence-based practice guidelines in chest medicine, have announced that Elsevier will publish the organization's flagship journal *CHEST* as of January 1, 2016. This significant and exciting piece of news that will positively affect the future of the journal is a licensing agreement, wherein CHEST retains all ownership of the journal, copyright, trademark, and editorial decision-making. Elsevier's role will be heavily focused on the business and operational aspects of publishing the journal and will provide significant resources to help us continue to take *CHEST* to a higher level.

"We are excited to begin this new relationship with Elsevier and we look forward to *CHEST*'s continued success under this collaboration," said Paul Markowski, CEO and Executive Vice President of the American College of Chest Physicians. "*CHEST* will remain a leading publication designed to aid clinicians in providing the best patient care possible."

Dr. Richard Irwin, Master FCCP, and Editor in Chief, said, "Our publishing agreement with Elsevier will allow *CHEST* to remain competitive, will help us to distribute research papers to a larger audience, and will allow us to better attract higher profile clinical research from around the world. We anticipate many enhancements to the journal, which will benefit our authors, members, and readers."

The relationship with Elsevier will allow *CHEST* to leverage the global capabilities of Elsevier, its ScienceDirect platform, and its new ClinicalKey service to distribute the journal to an even larger audience than ever and attract higher profile research from around the world.

CHEST Foundation grants – April 30th deadline is approaching!

Medical research grants have contributed to medical discoveries and innovations all over the world.

Milestone research projects, such as immunizations, pollutant quality control, 3D bioprinting technologies, and even public education programs and resources, have all been funded at one time or another by generous donations.

The results of those donations lead to amazing impacts on the medical profession and on patients' lives.



The CHEST Foundation contributes to advancing medical research and public education by providing our members with a variety of research grants and a community service grant.

Applications are now being accepted, and the April 30 deadline is approaching.

Apply today!
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 Help future grants by donating today!
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CHEST membership is moving forward to better serve you

TOMORROW > TODAY

We asked you, and you told us what you need to make your tomorrows greater than today.

That's why we're upgrading our membership philosophy and structure starting this May, allowing you to:

- **Collaborate more** with integrated programming and CHEST membership available to all members of your clinical care team.
- **Engage more** by choosing the membership level that gives you the benefits you want.
- **Achieve more** with streamlined access to our online systems, making it easier than ever to tap into the wealth

of resources CHEST offers you.

Learn more about the new membership model at chestnet.org/tomorrow. See videos of Dr. Curtis N. Sessler, FCCP, CHEST President, explaining why we're changing the membership model, and Paul Markowski, CHEST EVP/CEO, describing the benefits of the three levels of membership.

Get answers to commonly asked questions, and, if your question isn't answered there, submit a question of your own.

Visit now to find out how your CHEST membership can help make your tomorrows greater than today.

Catching up with Past Presidents: Dr. James B.D. Mark

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 (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with these past leaders to give us a look at what's new in their lives.

James B.D. Mark, MD, FCCP President 1994-1995

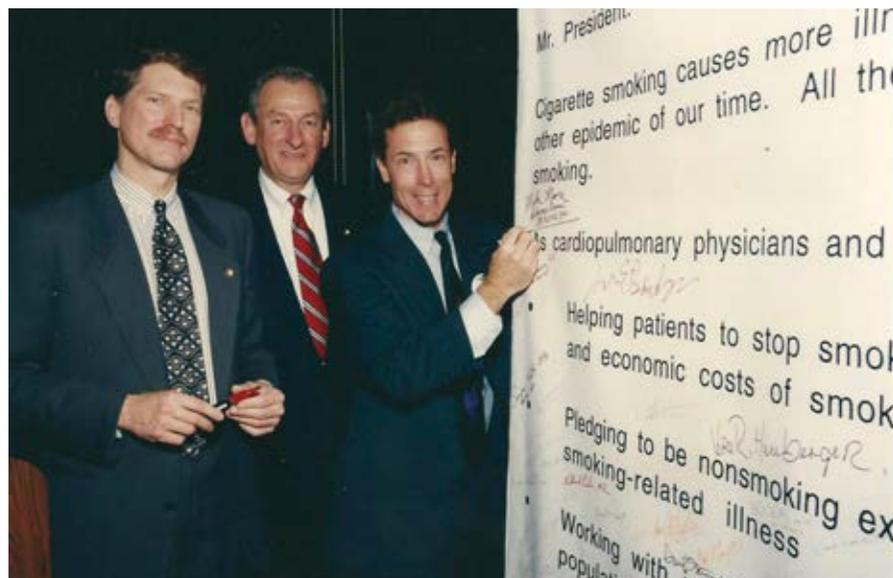
My presidential year began in New Orleans at CHEST 1994. The welcoming reception, which was Halloween-themed, started the year off with a bang. Attendees were encouraged to wear costumes and many did so. Two robbers, complete with trick-or-treat bags and masks, crashed the party and helped themselves to unattended purses and more. They were caught in the act by one of the guests and turned over to the New Orleans police. ... and the year just got better!

Two highlights were travel to the Asia-Pacific Congress on Diseases of the Chest in Hong Kong and to the

meeting of the European Respiratory Society in Barcelona. The delegation from the ACCP was well received at both meetings.

Memorable, also, was a leadership luncheon meeting with the American Thoracic Society in Seattle. Dr. Claude Lenfant, Director of the NHLBI, attended the luncheon. He said at the time that he had given many talks to lay and professional groups over the years and that during the question-and-answer periods, he had never had a question asked about lung disease, only heart disease, the clear implication being that we "Lungies" better get our message out to the public. Interacting with the staff of the ACCP and many members of leadership during the year was a stimulating and memorable experience.

I am currently Professor of Cardiothoracic Surgery, Emeritus at Stanford University School of Medicine. I achieved Emeritus status at Stanford in 1996, but continued to operate for another year and be active clinically for several more years. I no longer see patients but do attend conferences each week. I go to few professional meetings, national or



Dr. Mark (center), flanked by Tom Glide, of Blue Cross/Blue Shield of Minnesota (left), and Mike Moore, Attorney General of Mississippi (right), who was the Keynote Speaker at CHEST 1994.

international, but do travel with my wife and family. A highlight was a trip to Rwanda, Kenya, and Tanzania recently.

My exercise regimen includes walking, going to the gym for light workouts, and playing golf. Where but the Stanford Golf Course can a previous Heisman Trophy winner, Jim Plunkett, be in the foursome

ahead of you and an ex-Secretary of State, Condoleezza Rice, be in the one behind you?

*James B. D. Mark, MD, FCCP
Professor of Cardiothoracic Surgery,
Emeritus
Stanford University School of Medicine
President, American College of Chest
Physicians, 1994-1995*

Difficult Airway Management July 16-18



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Sarcoidosis patient education campaign

In honor of National Sarcoidosis Awareness month, the CHEST Foundation and Foundation for Sarcoidosis Research (FSR) have launched *Sarcoidosis: Seek Answers. Inspire Results.*, a nationwide campaign encouraging patients with sarcoidosis to take a proactive role in their treatment plan (www.stopsarcoidosis.org/patient-resources/what-is-sarcoidosis).

This rare, autoimmune disease, which affects the lungs in 90% of cases, can often mimic other conditions as well, further adding to the complexity of the disorder. For instance, sarcoidosis can mimic fungal or mycobacterial infections, chronic beryllium disease, hypersensitivity pneumonitis, rheumatologic syndromes, lymphoma, tumor-associated granulomas, pulmonary fibrosis, and more. Lung symptoms often include a cough that does not go away, shortness of breath, and chest pain. About one-third of patients will also experience nonspecific symptoms, such as fever, fatigue, weight loss, night sweats, and an overall feeling of ill health. Key diagnostic tools include chest radiographs, laboratory blood tests, breathing tests, and a biopsy.

Anyone can develop sarcoidosis; however, for reasons not yet understood by medical science, the condition is more prevalent among African-Americans and people of Northern European – particularly Scandinavian – descent.

Sarcoidosis most commonly occurs among people between the ages of 20 and 40.

If diagnosed and under good medical care, most cases of sarcoidosis have a positive prognosis and do not cause lasting damage to the body. However, 30% to 40% of people living with sarcoidosis have a persistent condition that may require personalized treatment – including co-consultation with other organ specialists, as indicated – to control symptoms.

To this end, the *Seek Answers. Inspire Results.* campaign encourages physician/patient dialogue, as well as treatment compliance. For educational tools to share with patients, including the “Sarcoid Five” – five questions designed to jumpstart physician/patient conversations – visit chestnet.org/sarcoid.

Patient education resources supported in part by a grant from Mallinckrodt Pharmaceuticals Autoimmune and Rare Diseases.

For further reading:

www.stopsarcoidosis.org/patient-resources/what-is-sarcoidosis/
www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/Default.htm#ceboxtext3
www.chestnet.org/Foundation/Patient-Education-Resources/Sarcoidosis
www.stopsarcoidosis.org/patient-resources/faqs/



This month in CHEST: Editor's picks

BY DR. RICHARD S. IRWIN, MASTER FCCP

Editor in Chief

Nighttime Intensive Staffing, Mortality, and Limits on Life Support: A Retrospective Cohort Study.

By Dr. M. P. Kerlin et al.

Hospital Discharges, Readmissions, and ED Visits for COPD or Bronchiectasis Among US Adults: Findings From the Nationwide Inpatient Sample 2001-2012 and Nationwide Emergency Department Sample 2006-2011.

By Dr. E. S. Ford

Ultrasound-Guided Medical Thoracoscopy in the Absence of Pleural Effusion

By Dr. G. Marchetti et al.



GIANTS IN CHEST MEDICINE

Honoring Dr. Jay A. Nadel

MEDICAL ETHICS The Uncommon Case of Jahi McMath

By Dr. J. M. Luce

EVIDENCE-BASED MEDICINE Executive Summary: Prevention of Acute Exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline (Podcast available.)

Prevention of Acute Exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline (Podcast available.)

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■ **Procedures for the Intensivist Including Bronchoscopy and Percutaneous Tracheostomy**
August 7-8

Who Should Attend?

Pulmonary and critical care fellows, physicians, advanced practice providers, intensivists, thoracic surgeons, respiratory therapists, nurses, physician assistants and health-care professionals interested in critical care and emergency medicine are encouraged to attend.

For complete course descriptions and additional information, visit chestnet.org/live-learning.

NETWORKS: Environmental health, palliative care, sleep medicine, respiratory care

Occupational and Environmental Health

Time to part the smoke screen: women and children first

Almost 3 billion individuals use solid fuels for heating and cooking, leading to very high levels of household air pollution. In a recent study comparing traditional clay “chulha” cook stoves and alternative cook stoves, there was a significant decrease in particulate matter (PM)_{2.5} and CO concentration (Muralidharan et al. *Int J Environ Res Public Health*. 2015;12[2]:1773).



DR. HARANATH

However, none of the cook stoves met the WHO standards that recommend a PM_{2.5} level below 25 µg/m³ particulate matter exposure. Indoor air pollution contributes to nearly 2 million deaths annually, with women disproportionately more affected, possibly from greater exposure. To address this major problem, the Global Alliance for Clean Cookstoves has a goal of reaching 100 million households by 2020 (Martin et al. *Science*. 2011;334[6053]:180). While outdoor air pollution is well-known, newer sources, like fracking, are only now being evaluated. The impact of air pollution and its management is inadequately studied despite the morbidity and mortality issues. In fact, searching clinicaltrials.gov using the keyword “air pollution” only shows 18 open studies (11 from North America). Encouragingly, there was recent evidence for reversal of decline in lung function in children who had a decrease in exposure to air pollutants (Gauderman et al. *N Engl J Med*. 2015;372[10]:905). Clearly, there is an urgent need for engagement on the air we breathe around the world. Our NetWork plans to have sessions on these themes at CHEST 2015.

Dr. Sai Praveen Haranath, MPH, FCCP
Steering Committee Member

Palliative and End-of-Life Care

Palliative care as a train station

Have you ever struggled to explain palliative care to a patient or family? My mentor taught me to describe palliative care as a train station. Typically, a patient’s symptoms and findings lead to tests and then treatments. Before they know it, patients are on an express train that is equipped to get them the best medical care possible. However, the train doesn’t feel like it’s under their control, and it has considerable momentum. In intensive care, the train is more like a roller coaster.



DR. KREGENOW

Similar to a train stopping to refuel and exchange passengers, a palliative care consult is a chance for a patient, family, and medical provider to get off the train and do two important things. First, we find the bathroom and sandwich shop, a metaphor for addressing symptoms. Second, we look at the map and examine where we’ve been and where we are headed. What was our destina-

tion? Is this train still headed in the right direction? Sometimes this visit to the train station leads to a change in itinerary; other times it just helps patients and families stay fed and warm. This pause helps everyone make sure the path we’re on is one that fits with the stated goals and keeps quality of life in perspective. Despite the growing awareness of palliative care, the average person has difficulty understanding the specialty until they experience it. With the train station metaphor, I find myself able to move past the description of palliative care and into a therapeutic conversation.

Dr. David Kregenow
Steering Committee Member

Sleep Medicine

OSA, snoring, and oral appliances

With increasing treatment options and a growing population of patients diagnosed with sleep-disordered breathing, the treatment of OSA is becoming more and more of a multidisciplinary field. Patients with OSA now have the options of CPAP therapy, oral appliances, negative oral pressure therapy, nasal expiratory airflow resistance devices, or surgical treatment options, including hypoglossal nerve stimulators and even weight loss surgery. Therefore, patients may be identified and managed by sleep specialists, dentists, surgeons, and other physicians. As a multidisciplinary approach becomes more common, updated guidelines will be necessary.



DR. DAS

Oral appliance therapy (OAT) to treat OSA has been an area of extensive research over the past several years. We have some data for improved cardiovascular outcomes with use of OAT for OSA. In 2002, the American Academy of Dental Sleep Medicine had 300 members, and now the association has over 2,700 members. More and more dentists are the initial caregivers who identify a patient at risk for OSA. Collaboration with sleep specialists should be encouraged in these situations for appropriate assessment of OSA severity and comorbid sleep disorders. Together, the sleep specialist and dentist can determine the best treatment for the patient and ensure adequate efficacy.

A new guideline for the treatment of OSA and snoring with oral appliances is forthcoming from the American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine. Physicians, dentists, and organizations, such as the Sleep NetWork Steering Committee of CHEST, have been asked to give input on the existing draft (www.aasmnet.org/articles.aspx?id=5362).

Dr. Aneesa Das, FCCP
NetWork Chair

Respiratory Care

Keeping the lunger out of the house: what’s new in preventing COPD readmissions?

In 2015, CMS added COPD to core measures used to calculate hospital risk-adjusted readmission rates. Up to 3% of total Medicare payments are at risk, and FY15 data indicate that three-fourths of eligible hospitals are being penalized, with an av-

erage penalty of 0.63% (<http://kaiserhealthnews.org/news/medicare-readmissions-penalties-2015>). COPD has readmission rates of up to 25% and is an independent risk factor for other medical readmissions.



DR. O’NEIL

Despite considerable interest in reducing COPD readmissions, there is little to guide pulmonologists and hospitals. CHEST and the Canadian Thoracic Society recently published guidelines for preventing AECOPD (Criner et al. *CHEST*. [Published ahead of print Oct 16, 2014]), although not specifically focused on readmissions. CHEST also recently published a systematic review of self-management following AECOPD (Harrison et al. *CHEST*. 2015;147[3]:646), and NAMDRC reported recommendations from a 2014 multisociety conference (www.namdr.org/pubs/HospitalReadmissions.pdf). Recent single institution studies (Hijjawi et al. *Postgrad Med*. [Published ahead of print Feb 17, 2015]) (Jennings et al. *CHEST*. [Published ahead of print Dec 24, 2014]), and an analysis of Medicare claims data (Shah et al. *CHEST*. [Published ahead of print Dec 24, 2014]) confirm the importance of COPD severity, comorbidities, and social/financial factors in readmissions. While AECOPD is the most common cause of readmission, half of the readmissions are nonpulmonary. The studies suggest that programs focused only on pulmonary disease are unlikely to be successful and that a multidisciplinary approach also addressing financial and psychosocial issues is needed.

Current interest has focused on patient navigators. Nursing models applied to outpatient populations have demonstrated reductions in hospitalizations and ED visits but didn’t address readmissions (Dajczman et al. *Can Respir J*. 2013[5]:351). Preliminary data using respiratory therapists (RTs) as COPD navigators have shown promise (<http://respiratory-care-sleep-medicine.advanceweb.com/Features/Articles/COPD-Navigators.aspx>), but, clearly, additional work and innovative approaches will be needed to significantly reduce COPD readmissions.

The Respiratory Care NetWork will examine the role of the RT in preventing COPD readmissions with its featured speaker presentation at CHEST 2015 in Montréal.

Dr. Kevin O’Neil, FCCP
NetWork Chair

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Interested applicants may submit CV to Julia Lauver, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauver@cmhc.org. Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

Cardiac Intensivist

OPPORTUNITY IN SOUTH FLORIDA

Memorial Healthcare System is seeking critical care physicians, dedicated to night shifts, to join the critical care team. Successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high-quality, evidence-based care. Applicants must be BC/BE in critical care medicine. Previous experience in managing cardiac surgery patients is a plus but not a requirement. Physician(s) would have exposure to all aspects of the care of cardiac surgery patients, including mechanical devices, advanced heart failure patients, ECMO and transplant.

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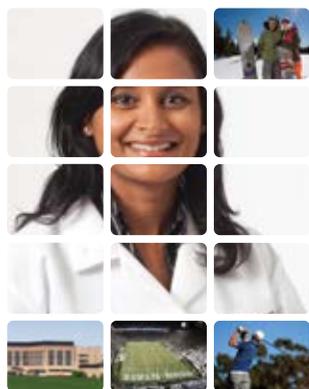
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Critical Care Medicine Nocturnist

OPPORTUNITY IN SOUTH FLORIDA

Memorial Healthcare System's Intensivist Program has expanded. The program is currently comprised of 23 full-time intensivists and five critical care ARNPs, providing 24/7 ICU coverage at multiple locations within the Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple board certifications including infectious diseases, pulmonology, surgery and neuro-critical care.

The available positions are full-time employed positions with competitive benefits and compensation package, sovereign immunity, paid CME and state-of-the-art equipment (including EPIC EHR, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds, etc.).

Qualifications & Responsibilities:

The program is seeking dedicated critical care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12-hour in-house shifts, 7pm to 7am, averaging approximately 15 shifts per month. The successful candidates will demonstrate excellent clinical skills, a broad knowledge base in critical care and dedication to providing high-quality, evidence-based care. Candidates must be BC/BE.



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Asthma exacerbations reduced by 20%

ICS/LABA from page 1

including a large safety study that addressed safety concerns associated with LABAs in the treatment of asthma.

At the March 19 joint meeting of the FDA's Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, the panels voted 16-4 that the efficacy and safety data supported the approval of both proposed doses in adults.

Many panelists noted the benefit of having a once-daily inhaled treatment to treat asthma, which could improve compliance. Most agreed that the efficacy data in adults provided a substantial amount of evidence that the two doses had a "clinically meaningful benefit" in adults, with beneficial effects on lung function and exacerbation rates.

But the panelists voted 19-1 that the data did not support approval in adolescents aged 12-17 years. Members expressed uncertainty about safety in adolescent subjects, who were studied in the same trials as were adults.

In addition, study data indicated that the combination's beneficial effects were no better than those of fluticasone alone, panelists said. They also noted a numerical imbalance in hospitalizations among adolescents in a large safety study, and they pointed to the availability of other treatments for that age group.

Panelists voting no also said the efficacy results in adolescents were inconsistent, with "no clear trends in the positive direction," as one panelist noted. Furthermore, there was no evidence that the combination of fluticasone and vilanterol at either dose was more effective than the ICS alone on forced expiratory volume in 1 second or asthma exacerbations.

Panelists also cautioned that the positive results in adults, who made up the majority of patients enrolled in the studies, could not be extrapolated to adolescents. Thus, there was a need for a separate safety and efficacy study in adolescents.

"At least in the adults, it offers something, perhaps the additional benefit of better compliance," said the panel chair, Dr. Erik Swenson, professor of medicine and physiology, pulmonary and critical care medicine, University of Washington, Seattle.

The combination also was superior at both doses at improving lung function and reducing exacerbations.

But among patients age 12-17 years, "there seems to be no obvious superiority and possibly inferiority against just fluticasone alone," Dr. Swenson said.

Considering that results of large, ongoing LABA safety trials may soon become available, "I don't feel comfortable adding a new LABA to the mix right now," said Dr. Judith Kramer, professor emerita of medicine, Duke University, Durham, N.C., who voted against approval both for pediatric and adult patients.

Because it is taken once a day, the combination's main advantage would be adherence, Dr. Kramer added. But "it's not adding any major new therapeutic benefit, and there is the safety concern in the adolescents, and there may well be off-label use."

Given longstanding concerns about serious asthma-related events associated with LABAs – particularly in pediatric and black patients – the FDA has required manufacturers to conduct postmarketing safety studies evaluating the risks of LABAs when added to an ICS.

Those studies include a GSK study of more than

11,000 patients aged 12 years and older evaluating the safety of Advair, a combination of fluticasone and the LABA salmeterol. Results from that study could be available in early 2016.

For the fluticasone-vilanterol asthma indication, GSK submitted the results of two 12-week and one 24-week lung function studies, enrolling a total of about 2,200 patients whose mean age was 44 years (about 8% were aged 12-17 years).

Another study evaluated the time to first asthma exacerbation in more than 2,000 patients, which included almost 300 patients aged 12-17 years. In that study, the risk of asthma exacerbations was reduced by about 20% among those on the combination, compared with those on fluticasone alone. There were no intubations or deaths from asthma exacerbations.

But in a subgroup analysis of patients aged 12-17 years, conducted by the FDA, the risk of asthma exacerbations was higher among those treated with fluticasone-vilanterol, compared with patients 18 years and older.

In addition, an FDA meta-analysis of asthma-related serious adverse events in the four studies found a numerical imbalance in hospitalizations among adolescents: four hospitalizations among those on the combination drug, but none on fluticasone alone.

If approved, fluticasone-vilanterol would be the first once-daily inhaled ICS/LABA combination treatment for asthma. Fluticasone (100 mcg and 200 mcg) is approved for treating asthma. Unlike the LABAs salmeterol and formoterol, however, vilanterol is not approved as a single agent. Vilanterol (as part of the combination product) would be the first new LABA approved for asthma in 15 years.

The FDA usually follows the recommendations of its advisory panels; a decision is expected by April 30. Panelists had no disclosures.

emechcatie@frontlinemedcom.com

FDA approves miniature heart pump for high-risk PCI

BY ELIZABETH MECHCATIE
Frontline Medical News

A miniature heart pump has been approved by the Food and Drug Administration to "help certain patients maintain stable heart function and circulation during certain high-risk percutaneous coronary intervention (HRPCI) procedures," the agency has announced.

The Impella 2.5 System, manufactured by Abiomed, is "intended for temporary use by patients with severe symptomatic CAD [coronary artery disease] and diminished (but stable) heart function who are undergoing HRPCI but are not candidates for surgical coronary bypass treatment," the FDA's statement said.

"Use of the Impella 2.5 System is intended to prevent episodes of unstable heart function, including unstable blood pressure and poor circulation, in patients who are at high

risk for its occurrence," Dr. William Maisel, acting director of the Office of Device Evaluation in the FDA's Center for Devices and Radiological Health, said.

Approval was based on the PROTECT II study and observational data from the USpella Registry.

"The overall data provided evidence that, for patients with severe CAD and diminished heart function, the temporary circulatory support provided by the Impella 2.5 System during an HRPCI procedure may allow a longer and more thorough procedure by preventing episodes of hemodynamic instability ... due to temporary abnormalities in heart function," the FDA statement said. In addition, "fewer later adverse events" such as the need for repeat HRPCI procedures, "may occur in patients undergoing HRPCI with the pump compared to patients undergoing HRPCI with an intra-aortic balloon



COURTESY: ABIOMED

pump," according to the FDA.

The system can be used as an alternative to the intra-aortic balloon pump without significantly increasing the safety risks of the HRPCI procedure. As a postmarketing requirement, the manufacturer will conduct a single-arm study of the device in high-risk PCI patients, the company said in a statement.

The wording of the approved indication is as follows, according to Abiomed: "The Impella 2.5 is a temporary (less than or equal to 6 hours) ventricular support device indicated for use during high-risk

PCI performed in elective or urgent hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. Use of the Impella 2.5 in these patients may prevent hemodynamic instability that may occur during planned temporary coronary occlusions and may reduce peri- and postprocedural adverse events."

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