Worse outcomes with video laryngoscopy

When used in intensive care units, video laryngoscopy did not improve the chances of successful intubation on the first try, compared with direct laryngoscopy, and was associated with a significantly higher risk of severe life-threatening complications, researchers reported.

In a multicenter, randomized trial of 371 patients, first-pass intubation rates did not differ significantly whether video or direct laryngoscopy was used, at 67.7% and 70.3%, respectively, Jean Baptiste Lascarrou, MD, of District Hospital Centre, La Roche-sur-Yon, France, and his associates wrote. Meanwhile, the combined rate of death, cardiac arrest, severe cardiovascular collapse, and hypoxemia was 9.5% with video laryngoscopy and just 2.8% with direct laryngoscopy, a significant difference (JAMA. 2017 Jan 24;317[5]:483-93).

“Improved glottis visualization with video laryngoscopy did not translate into a higher success rate for first-pass intubation, because tracheal catheterization under indirect vision was more difficult, in keeping with earlier data,” the researchers concluded. “Further studies are needed to assess the comparative effectiveness of these two strategies in different clinical settings.”

Updated guidelines for the diagnosis and treatment of cystic fibrosis (CF) include two major changes.

The first important update is that clinicians use the latest classifications of the specific CF transmembrane conductance regulator (CFTR) gene mutations, from the Clinical and Functional Translation of CFTR (CFTR2) database, to aid with making a CF diagnosis in any patient, newborn to adult. The other of these changes relates to the chloride concentration level used to confirm CF diagnosis through a sweat test. Under the new guidelines, the sweat chloride threshold for “possible” CF or a CF-related disease was reduced to 30 mmol/L of chloride concentration from 40 mmol/L across all ages. The guidelines, written by an international team of collaborators and published by the Cystic Fibrosis Foundation, are available online in the Journal of Pediatrics (2017 Feb;181[suppl]:S4-15. doi: 10.1016/j.jpeds.2016.09.064). Since its inception in See CF guidelines • page 4

Watch and wait often better than resecting in ground-glass opacities

Three years of follow-up is adequate for partially solid ground-glass opacity lesions that do not progress, while pure ground-glass opacity lesions that show no progression may require further follow-up care, a study suggests.

The results of the study strengthen the argument for taking a “watch and wait” approach, and raise the question of whether patient outcomes can be improved without more precise diagnostic criteria, said study author Shigei Sawada, MD, PhD, a researcher at the Shikoku Cancer Center in Matsuyama, Japan, and his colleagues. They drew these conclusions from performing a long-term outcome investigation of 226 patients with pure or mixed ground-glass opacity lesions that do not progress (JAMA. 2017 Nov 28;318[22]:2421-9. doi: 10.1001/jama.2017.18158). Since its inception in See Ground-glass opacities page 7

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

ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

* The efficacy of Esbriet was evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)

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

© 2016 Genentech USA, Inc. All rights reserved. ESB/021215/0039(1)a(1) 04/16

DEMONSTRATED EFFICACY*

- Esbriet had a significant impact on lung function vs placebo in ASCEND2,3
  —48% relative reduction in risk of a meaningful decline in lung function (≥10% decline in %FVC) at 52 weeks for patients on Esbriet vs placebo (17% vs 32%; 15% absolute difference; P<0.001)
  —2.3× as many patients on Esbriet maintained their baseline function at 52 weeks vs placebo (23% vs 10% of patients; 13% absolute difference; P<0.001)
- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND2,3
- No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 0062,4
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)

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

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

WORLDWIDE PATIENT EXPERIENCE
- Esbriet has been approved outside the US since 2011
- More than 27,000 patients have taken pirfenidone worldwide

Genentech
A Member of the Roche Group
© 2016 Genentech USA, Inc. All rights reserved. ESB/021215/0039(1)a(1) 04/16
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 18.6% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

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

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

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

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

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

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

Esbriet should be used with caution in patients with mild (CLcr 50-80 mL/min), moderate (CLcr 30-50 mL/min), or severe (CLcr 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.

Genotyping is recommended

CF guidelines from page 1

2008, the CFTR2 project has described over 300 specific variants in the CF gene and their various functional and clinical impacts. The project involves amassing phenotypic and genotypic information from patient registries to collect, quantify, and describe mutations reported in individuals with CF. Such mutations are categorized as CF causing, carrying a variety of potential clinical consequences; non–cystic fibrosis causing; or unknown. The previous guidelines, written in 2008, relied on a 23-mutation panel from the American College of Medical Genetics and Genomics and the American Congress of Obstetricians and Gynecologists.

“We’ve more precisely defined what cystic fibrosis is,” Patrick R. Sonny, MD, assistant professor of medicine at Johns Hopkins University, Baltimore, and coauthor of the guidelines, said in a statement. “The stakes in categorizing a mutation are particularly high. For example, claiming that a mutation 100% caus-
7 DRUG INTERACTIONS

7.1 CYPIA2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYPIA2 with minor contributions from other CYP isoenzymes including CYPIB1C9, 2C9, 2D6 and 2E1.

Strong CYPIA2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYPIA2 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 CYPIA2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYPIA2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see Doseage and Administration section 2.4 in full Prescribing Information].

Moderate CYPIA2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYPIA2) 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 Doseage 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 CYPIA2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYPIA2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYPIB1C9, 2C9, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYPIA1 Inducers

The concomitant use of ESBRIET and a CYPIA1 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYPIA1 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYPIA1 inducer [see Clinical Pharmacology section 12.3 in full Prescribing Information].

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. However, 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 dosages up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses of 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

8.2 Nursing Mothers

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

8.3 Pediatric Use

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

8.4 Geriatric Use

The stakes in categorizing a mutation are particularly high. A person’s reproductive decisions, for example, might be affected by learning he could have a child with a mutation that is 100% causing cystic fibrosis, according to a statement from Dr. Sosnay.

es cystic fibrosis may affect people’s reproductive decisions if they believe their child will have the mutation.”

In the CFTR2 project, the “disease-liability” of each mutation is evaluated through a combination of sweat chloride and functional activity identified in cell-based systems, according to a supplement published simultaneously with the updated guidelines (J Pediatr. 2017 Feb;181[suppl.],S32-7. doi: 10.1016/j.jpeds.2016.09.068). Data from this project led to the discovery of a cohort of 746 persons diagnosed with CF despite sweat chloride levels less than 60 mmol/L. These findings were the basis for the guideline authors’ decision to lower the threshold of chloride concentration in sweat in order for an individual to be considered having a possible CF diagnosis, according to the supplement.

The guidelines include 27 approved consensus statements spanning four overlapping categories, and applying to screened and non-screened populations; newborn screened populations and fetuses undergoing prenatal testing; infants with an uncertain diagnosis and designated as having either CFTR gene-related metabolic syndrome or being CF-screen positive, inconclusive diagnosis; and nonscreened patients who present with symptoms, including children before newborn.
“Understanding a disease’s genetic epidemiology helps identify patients who may be subject to the clinical manifestations of that disease. As we learn more about the variants in cystic fibrosis genetics and the functional and clinical impacts, there is a greater opportunity to better characterize a CF mutation,” Dr. De Palo said.

The updated guideline authors recommend avoiding the use of terms such as “atypical” or “nonclassical” CF, as there is no consensus on the specific taxonomy of CF, since the genetic data are still emerging.

When a newborn test is administered, the guidelines warn that the heterogeneous nature of newborn screening often leads to false-positive results, thus the need for the sweat test. Although obtaining an adequate sweat specimen for chloride measurement can be difficult, the authors say it is possible, especially in full-term infants aged 1 month. Repeat sweat testing is recommended, as is nasal potential difference and intestinal current measurement in some cases.

Another change to the guidelines is that newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may now be designated as having CFTR-related metabolic syndrome/CF-screen positive inconclusive diagnosis (CRMS/CFSPID), instead of CFTR-related metabolic syndrome or CF-screen positive, inconclusive diagnosis. Regarding changes to screening for CRMS/CFSPID, the older guidelines called for such an assessment by age 2 months, repeated every 6-12 months, while the new guidelines say their recommendation on the duration and frequency of follow-up “remains to be determined.”

The authors of the first supplement decry the lack of standardized CF diagnostic criteria for those diagnosed with CF outside of the neonatal period, and urge clinicians to rely on clinical evidence including organ pathologies typical in CF, such as bronchiectasis or pancreatic insufficiency, along with testing for the presence of CFTR dysfunction with sweat chloride testing, CFTR molecular genetic analysis, or CFTR physiologic tests. In contrast, the second supplement states that “clinical suspicion should always take precedence” in making a CF diagnosis for individuals in this age group.

“Understanding a disease’s genetic epidemiology helps identify patients who may be subject to the clinical manifestations of that disease. As we learn more about the variants in cystic fibrosis genetics and the functional and clinical impacts, there is a greater opportunity to better characterize a CF mutation,” noted Vera A. De Palo, MD, MBA, FCCP, of Signature Healthcare in Brockton, Mass. “These guidelines will bring that enhanced knowledge to providers identifying and caring for cystic fibrosis patients.”

Dr. Sonny and Philip M. Farrell, MD, PhD, a coauthor of the guidelines, received funds from the Cystic Fibrosis Foundation, where guideline coauthor Terry B. White, PhD, is an employee. Kris De Boeck, MD, a coauthor of the first supplement, receives funding from Vertex Pharmaceuticals, Abylnx, Apalix, Galapagos, Gilead, Pharmaxis, and PTC Therapeutics. The guideline and supplements’ other authors have no disclosures.

wmcknight@frontlinemedcom.com
On Twitter @whitneymcKnight
Eric Gartman, MD, FCCP, comments: This study provides further support that the biology of ground-glass and part-solid nodules is different from fully solid nodules – and we should not be in a rush to resect these lesions. While the recommendations are likely to evolve over time as more information becomes available, this conservative approach toward nonsolid nodules is currently adopted in the Lung-RADS guidelines. Invasive action on these nodules is based on solid component size and growth, and usually the interval for following them once they have demonstrated early stability is annually. The optimal duration of follow-up is still in question, but ceasing follow-up for all part-solid nodules at 3 years likely is premature given the variable slow progression these nodules exhibit.

continued on page 12

AEBs higher after video procedure

Intubation from page 1

settings and among operators with diverse skill levels.7

Intubation in the ICU carries an inherently high risk because patients are often acutely unstable, and the intubating clinician is usually a non-expert, the investigators noted. At the same time, the procedure must be done quickly to prevent aspiration because patients usually have not fasted. Care bundles and training on simulators have improved safety, but ICU intubations remain riskier than those done in the operating room. 

Observational studies and smaller trials in ICUs seemed to support video laryngoscopy over the Macintosh laryngoscope, but raised questions about intubation time and mortality, the investigators noted. To help resolve these issues, they randomly assigned adults needing orotracheal intubation at seven ICUs in France to either video or direct Macintosh laryngoscopy, and followed them for 28 days. Patients averaged 63 years of age, and 37% were women. For both arms, residents performed the initial intubation attempt in about 80% of cases, and successful intubation usually took 3 minutes. Video laryngoscopy did not significantly increase the combined risk of esophageal intubation, aspiration, arrhythmia, or dental injury (5.4% versus 7.7% for direct laryngoscopy). But the only death in the study occurred after video laryngoscopy, and there were four cardiac arrests after video laryngoscopy and none after direct laryngoscopy, the researchers said. Furthermore, the rate of severe hypoxemia was nearly six times higher after video laryngoscopy than with direct laryngoscopy, and the rate of hypotension was twice as high.

The researchers did not identify predictors of life-threatening complications with video laryngoscopy, but hypothesized that being able to clearly visualize the glottis might create “a false impression of safety,” especially among nonexperts. In addition, poorer alignment of the pharyngeal axis, laryngeal axis, and mouth opening despite good glottis visualization by video laryngoscopy can lead to mechanical upper airway obstruction and faster progression to hypoxemia,” they wrote.

“As healthcare providers, we strive to continuously improve outcomes for our patients. As techniques and technologies continue to improve, clinical study permits us to evaluate new strategies,” noted Vera A. De Palo, MD, MBA, FCCP, of Signature Healthcare in Brockton, Mass.

“While this study demonstrated no difference in first-pass orotracheal intubation rates between video laryngoscopy and direct laryngoscopy, the reported association of higher rates of pharyngeal soft tissue injury and longer intubation times in patients undergoing video laryngoscopy as compared with direct laryngoscopy.

The view during video laryngoscopy can also create a cognitive blind spot: Laryngoscopists may fail to abort a laryngoscopy attempt in a timely manner because they have such a clear view of the larynx.

Brian O’Gara, MD, and Daniel Talman, MD, of Harvard Medical School, Boston, and Samuel Brown, MD, MS, of the University of Utah School, Murray, Utah, made these comments in an accompanying editorial (JAMA. 2017 Feb 7; doi: 10.1001/jama.2016.21036). None of the authors had relevant financial disclosures.

CT exam frequency

Ground-glass opacities from page 1

glass opacity lesions shown by CT imaging to be 3 cm or less in diameter.

Once established that the disease has stabilized in a pure or mixed ground-glass opacity lesion, “the frequency of CT examinations could probably be reduced or ... discontinued,” the investigators wrote. The study is published online in Chest (2017;151[2]:308-15).

Because ground-glass opacities often can remain unchanged for years, reflexively choosing resection can result in a patient’s being overtreated. Meanwhile, the use of increasingly accurate imaging technology likely means detection rates of such lesions will continue to increase, leaving clinicians to wonder about optimal management protocols, particularly since several guidance documents include differing recommendations on the timing of surveillance CTs for patients with stable disease. The study includes 10-15 years of follow-up data on the 226 patients, registered between 2000 and 2005. Across the study, there were nearly twice as many women as men, with all an average age of 61 years. About a quarter had multiple ground-glass opacities; about a quarter also had partially consolidated lesions. Of the 124 patients who’d had resections, all but one was stage IA. The most prominent histologic subtype was adenocarcinoma in situ in 63 patients, followed by 39 patients with minimally invasive adenocarcinomas, and 19 with lepidic predominant adenocarcinomas. Five patients had papillary-predominant adenocarcinomas. Roughly one-quarter of the cohort did not receive follow-up examinations after 68 months, as their lesions either remained stable or were shown to have reduced in size. Another 45 continued to undergo follow-up examinations.

After initial detection of a pure ground-glass opacity, the CT examination schedule was every 3, 6, and 12 months, and then annually. After detection of a mixed ground-glass opacity, a CT examination was given every 3 months for the first year, then reduced to every 6 months thereafter. In patients with stable disease, the individual clinicians determined whether to obtain additional CT follow-up imaging.

A ground-glass lesion was determined to have progressed if the diameter increased, as it did in about a third of patients; or, if there was new or increased consolidation, as there was in about two-thirds of patients. The table of consolidation/tumor ratios (CTR) used included CTR zero, also referred to as a pure ground-glass lesion; CTR 1-25; CTR 26-50; and CTR equal to or greater than 51. When there were multiple lesions, the largest one detected was the target. All cases of patients with a CTR of more than zero were identified within 3 years, while 13.6% of patients with a CTR of zero required more than 3 years to identify tumor growth. Aggressive cancer was detected in 4% of patients with a CTR of zero and in 70% of those with a CTR greater than 25% (P less than .001). Aggressive cancer was seen in 46% of those with consolidation/tumor ratios that increased during follow-up and in 8% of those whose tumors increased in diameter (P less than .001).

Video laryngoscopy creates blind spots

T he results of this trial illustrate the fundamental problem with video laryngoscopy: It generates excellent views of the larynx but may not facilitate tracheal intubation. The use of video laryngoscopy can lead to the creation of blind spots, both visual and cognitive. Because the lens of the laryngoscope is located at the tip of the device, the pharynx and hypopharynx are not visualized during video laryngoscopy. Manipulating the endotracheal tube into view therefore occurs within this blind spot, and this can be difficult depending on the patient’s pharyngeal anatomy. This phenomenon has been linked to higher rates of pharyngeal soft tissue injury and longer intubation times in patients undergoing video laryngoscopy as compared with direct laryngoscopy.

The view during video laryngoscopy bears further study.”

Centre Hospitalier Département de la Vendée sponsored the study. Dr. Lascarrou reported having no relevant conflicts of interest. Four coinvestigators disclosed ties to Fisher & Paykel, LFB, Merck Sharp & Dohme, Astellas, Basilea Pharmaceutica, Gilead, Alexion, and Cubist. The remaining coinvestigators had no disclosures.

Eric Gartman, MD, FCCP, comments: This study provides further support that the biology of ground-glass and part-solid nodules is different than fully solid nodules – and we should not be in a rush to resect these lesions. While the recommendations are likely to evolve over time as more information becomes available, this conservative approach toward nonsolid nodules is currently adopted in the Lung-RADS guidelines. Invasive action on these nodules is based on solid component size and growth, and usually the interval for following them once they have demonstrated early stability is annually. The optimal duration of follow-up is still in question, but ceasing follow-up for all part-solid nodules at 3 years likely is premature given the variable slow progression these nodules exhibit.

continued on page 12
WARNING: Long-acting beta₂-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

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

BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD. It is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNING, on the adjacent pages.
placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

• Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated

• Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol

• Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta-agonists

• The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents

• Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD

• Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting beta₂-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

† Demonstrated in two 24-week efficacy and safety studies in patients with moderate to very severe COPD (n=3699). The primary endpoint was change from baseline in trough FEV₁ at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; P<0.001 for all treatment comparisons.‡ Statistically significant results were also seen in Trial 2.

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

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

Cessating Conditions

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

Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see Clinical Pharmacology (12.2) in the full Prescribing Information]. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

Adverse Reactions

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

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

- Paradoxical bronchospasm [see Warnings and Precautions (5.4) in the full Prescribing Information]
- Hypersensitivity reactions [see Contraindications (4), Warnings and Precautions (5.3) in the full Prescribing Information]
- Cardiovascular effects [see Warnings and Precautions (5.6) in the full Prescribing Information]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.9) in the full Prescribing Information]
- Worsening of urinary retention [see Warnings and Precautions (5.10) in the full Prescribing Information]

Clinical Trials Experience

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

The clinical program for BEVESPI AEROSPHERE included 4,911 subjects with COPD in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,810, respectively). Of the 3,716 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV₁) was 51% (range: 18% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%). Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BEVESPI AEROSPHERE (n=1,036)</th>
<th>Glycopyrrolate 18 mcg BID (n=890)</th>
<th>Formoterol Fumarate 9.6 mcg BID (n=890)</th>
<th>Placebo (n=443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>2.6</td>
<td>1.8</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Urogenital tract infection</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

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

Indications and Usage

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the treatment of arthritis. The effectiveness and safety of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma [see Warnings and Precautions (5.1) in the full Prescribing Information].

Dosage and Administration

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

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

BEVESPI AEROSPHERE is intended to be used on an as-needed basis in the relief of acute asthma attacks. The first BEVESPI AEROSPHERE spray should be used 5 minutes following the last BM. BEVESPI AEROSPHERE should be used 2 minutes following the last BM. Rhythm of formoterol fumarate, like other beta-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, like other beta-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cessating Conditions

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

Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

Adverse Reactions

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. BEVESPI AEROSPHERE is not indicated for the treatment of asthma. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cardiovascular Effects

Formoterol fumarate, like other beta-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

Cessating Conditions

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

Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. If such effects occur, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.
Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparring Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparring 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. Approximately 17% of subjects were taking non-potassium sparring diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparring diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparring diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparring diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of other beta when administered concomitantly. 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 alternative alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

Glycopyrrolate: There was no evidence of teratogenic effects in rats and rabbits at approximately 18,000 and 270 times, respectively, the maximum recommended human daily inhalation dose (MRHID) in adults (on a mg/m² basis at a maternal oral dose of 65 mg/kg/day in rats and at a maternal in utero injection dose of 5.5 mg/kg in rabbits).

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

Formoterol Fumarate: Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats and teratogenic in rabbits. These effects were observed at approximately 1,500 (rats) and 61,000 (rabbits) times the MRHID (on a mg/m² basis at maternal oral doses of 3 mg/kg/day and above in rats and 60 mg/kg/day in rabbits). Umbilical hernia was observed in rat fetuses at approximately 1,500 times the MRHID (on a mg/m² basis at maternal oral doses of 3 mg/kg/day and above). Prolonged pregnancy and fetal brachygnathia was observed in rats at approximately 7600 times the MRHID (on a mg/m² basis at an oral maternal dose of 15 mg/kg/day in rats). In another study in rats, no teratogenic effects were seen at approximately 600 times the MRHID (on a mg/m² basis at maternal injection doses up to 1.2 mg/kg/day in rats). Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHID (on a mg/m² basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3800 times the MRHID (on a mg/m² basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Based on available data, no adjustment of the dosage of BEVESPI AEROSPHERE in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. The confirmatory trials of BEVESPI AEROSPHERE for COPD included 1,680 subjects aged 65 and older and, of those, 1,591 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

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

Renal Impairment

Formal pharmacokinetic studies using BEVESPI AEROSPHERE have not been conducted in patients with renal impairment. In patients with severe renal impairment (creatinine clearance of ≤30 mL/min/1.73 m²) or end-stage renal disease requiring dialysis, BEVESPI AEROSPHERE should be used if the expected benefit outweighs the potential risk. [see Clinical Pharmacology (12.3) in the full Prescribing Information].

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta,-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate. BEVESPI, AEROSPHERE™ and BEVESPI AEROSPHERE™ are trademarks of the AstraZeneca group of companies. ©AstraZeneca 2016

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: Aventis Pharma LTD, Holmes Chapel CW488E, United Kingdom

04/16 3309803 11/16
Sarcoidosis doubled risk of hospitalization for infection

BY WHITNEY MCKNIGHT
Frontline Medical News

Persons with sarcoidosis were found to have double the risk of hospitalization, compared with age-matched controls in a population-based cohort study that also linked glucocorticoid use with an increased risk of hospitalization in this group.

Using data from the Rochester Epidemiology Project record-linkage system, Patompong Ungprasert, MD, an assistant professor of medicine at the Mayo Clinic in Rochester, Minn., and his colleagues identified 345 incident cases of sarcoidosis recorded between 1976 and 2013, confirmed by individual medical records (Ann Am Thorac Soc. 2017 Feb 8. doi: 10.1513/AnnalsATS.201610-750OC). With use of random selection, each patient was age and sex matched with sarcoidosis-free controls taken from the same database. Medical records across the study were examined for community-acquired infections requiring hospitalization that occurred after the index date or the date of diagnosis.

The nearly all-white population across the study had an average age of 45 years and was evenly divided according to sex. The mean length of follow-up was 15 years for the study arm, and 16.8 years for controls.

Risk factors for infection, such as smoking status, obesity, diabetes, and others were also matched, although there were nearly twice as many controls who smoked, compared with study subjects – 36% vs. 19% (P less than .001) – whereas the obesity rate was twice as high in the study arm: 41% vs. 21% (P less than .001). Results were adjusted for at least 3 years in patients with pure ground-glass lesions and between 3 and 5 years in the other CTR groups with nodules measuring 8 mm or less. The National Comprehensive Cancer Network guideline advises low-dose CT scanning until a patient is no longer eligible for definitive treatment.

Dr. Ungprasert and his colleagues did not use an exact criterion for tumor growth in their study; such as a precise ratio of increase in size or consolidation, in part because at the time of the study the most common form of CT evaluation was visual inspection; they reported that tumors exhibiting growth most commonly increased between 2 and 3 mm in either size or consolidation. “Evaluations based on visual inspections can be imprecise, and different physicians may arrive at different judgments,” the investigators wrote. However, [the use of] computer-aided diagnosis systems are not yet commonly applied in clinical practice.”

Although imaging should have guided the decision to resect, according to Dr. Sawada and his coauthors, two-thirds of patients in the study were given the procedure even though their lesions were not shown by CT scans to have progressed. This was done either at the patient’s request, or per the clinical judgment of a physician.

Although the study “represents a major advance,” according to Frank C. Detterbeck, MD, FCCP, surgical director of thoracic oncology at Yale University, New Haven, Conn., who wrote an editorial accompanying the study, the results should spur the field to get more specific, and question whether a 3-year window was enough. “This seems counterintuitive given the chance of it becoming an invasive cancer,” Dr. Detterbeck wrote, indicating that not rushing to resection should mean more use of CT. “We should just look at what is already in front of our eyes: the radiographic features of [ground-glass nodules] are highly predictive of biological behavior. It will be hard to do better than this.”

Also becoming more specific about changing CTRs would be helpful in developing management protocols, according to Dr. Detterbeck. “In my opinion, we need to start factoring in the rate of change. A gradual 2 mm increase in size over a period of 5 years may not be an appropriate trigger for resection.”

Neither the investigators nor the editorial writer had any relevant disclosures.

wmcknight@frontlinemedcom.com
On Twitter @whitneymcknight
SAVR an option for elderly with aortic stenosis

BY DOUG BRUNK
Frontline Medical News

HOUSTON – Surgical aortic valve replacement (SAVR) can be performed in intermediate-risk elderly patients with an operative mortality rate of 4.1%, which is better than expected, according to results from a large multicenter analysis. However, the rate of in-hospital stroke was 5.4%—twice what was expected.

“This is most likely secondary to neurologic assessment [that was] conducted for all patients postoperative-ly,” Vinod H. Thourani, MD, said at the annual meeting of the Society of Thoracic Surgeons.

The findings come from an in-depth analysis of SAVR outcomes in patients who participated in the Placement of Aortic Transcatheter Valves trial, known as PARTNER 2A. Conducted from December 2011 to November 2013, PARTNER 2A evaluated 2,032 medium-risk patients with aortic stenosis who were randomized to SAVR or transcatheter aortic valve replacement (TAVR) in 57 North American centers and found no significant difference in the 2-year rate of death or disabling stroke (N Engl J Med. 2016 Apr 28;374(9):1609-20). Dr. Thourani’s analysis focused on the 937 patients who underwent SAVR. The main objectives were to describe operative mortality and hospital morbidity compared with STS benchmarks, describe time-related mortality and stroke including preoperative predictors for these outcomes, evaluate the effect of concomitant procedures on mortality and hospital morbidities and evaluate longitudi-nal valve performance after SAVR.

The average age of these patients was 82 years, 45% were female, and their mean STS risk score was 5.8. In addition, 26% had prior coronary artery bypass (CABG) surgery, 10% had a previous stroke, and 12% had previous pacemaker placement. Of the 30% of patients with chronic obstructive pulmonary disease, 9.6% were oxygen dependent going into the operating room, reported Dr. Thourani, one of the PARTNER 2A investigators, and a cardiothoracic surgeon at Emory University, Atlanta.

Most of the patients (85%) had a full sternotomy, while 15% had a mini sternotomy. Isolated AVR was done in 79% of patients, 15% of patients had AVR plus CABG, and 6% had AVR and other concomitant procedures. The mean coronary bypass time for isolated AVR was 98 minutes, and rose to a mean of 129 minutes when a concomitant procedure was added. The mean cross-clamp time was 69 minutes, and rose to a mean of 95 minutes when a concomitant procedure was added.

The investigators observed that all-cause operative mortality was 4.1%, which is lower than STS predicted-risk models. At the same time, mortality for AVR plus a concomitant procedure was 5%, followed by isolated AVR (4.2%) and AVR plus CABG plus a concomitant procedure (2.9%). The rate of in-hospital stroke was 5.4% and the rate of in-hospital deep sternal wound infection was 0.8%. At 2 years postoperatively, mortality was 17% among those who underwent isolated AVR, 18% among those who underwent AVR plus CABG, and 21% among those who underwent AVR plus a concomitant procedure, differences that did not reach statistical signi-ficance. The rate of stroke at 2 years also was similar between groups: 12% among those who underwent isolated AVR, 11% in those who underwent AVR plus a concomitant procedure, and 8.2% in those who underwent AVR plus CABG.

The main risk factor for early death after SAVR was longer procedure time (P less than .0001), while risk factors for later deaths included cachenxia (P = .02), lower ejection fraction (P = .01), higher creatinine (P = .03), coronary artery disease (P = .03), and smaller protheses (P = .01).

Dr. Thourani and his associates also found that 33% of patients had severe prosthesis-patient mismatch, yet they had survival rates similar to the rates of those without severe prosthesis-patient mismatch.

“From this adjudicated, prospec-tively collected data in the contem-porary era, SAVR can be performed in intermediate-risk elderly patients with mortality commensurate with national benchmarks,” he concluded. “Continued surveillance of these pa-tients remains extremely important.”

Dr. Thourani disclosed that he is a consultant for and has received research support from Edwards Life-sciences. Other authors of the study reported having numerous relevant financial disclosures.

dbrunk@frontlinemedcom.com

Can bioprosthetics work for large airway defects?

BY RICHARD MARK KIRKNER
Frontline Medical News

Large and complex airway defects that primary repair cannot fully close require alternative surgical approaches and techniques that are far more difficult to perform, but bioprosthetic materials may be an option to repair large tracheal and bronchial defects that has achieved good results, without postoperative death or defect recurrence, in a small cohort of patients at Massachusetts General Hospital, Boston.

Brooks Udelsman, MD, and coauthors reported their results of bioprosthetic repair of central airway defects in eight patients in the Journal of Thoracic and Cardiovascular Surgery (2016;152:1388-97). “Although our results are de-rived from a limited number of heterogeneous patients, they suggest that closure of non-circumferential large airway defects with bioprosthetic materials is feasible, safe and reliable,” Dr. Udelsman said. He previously reported the results at the annual meeting of the American Association for Thoracic Surgery, May 14-18, 2016, in Baltimore.

These complex defects typically exceed 5 cm and can involve communication with the esophagus. For repair of smaller defects, surgeons can use a more traditional approach that involves neck flexion, laryngeal release, airway mobilization, and hilar release, but in larger defects these techniques increase the risk of too much tension on the anastomosis and dehiscence along with airway failure. Large and complex defects occur in patients who have had a previous airway operation or radia-tion exposure, requiring alternative strategies, Dr. Udelsman and coauthors said. “Patients in this rare category should be referred to a high-volume center for careful evaluation by a surgeon experienced in complex airway reconstruction before the decision to abandon primary repair is made,” he said.

Among the advantages that bioprosthetic materials have over synthetic materials for airway defect repair are easier handling, minimal immunogenic response, and potential for tissue ingrowth, Dr. Udelsman and coauthors said.

All eight patients in this study, who underwent repair from 2008 to 2015, had significant comorbidities, including previous surgery of the trachea, esophagus, or thyroid. The etiology of the airway defect included HIV/AIDS-associated esophagitis,

Continued on page 18
Patients treated with ELIQUIS – There is no established way to reverse the anticoagulant effect of ELIQUIS increases the risk of bleeding and can cause

WARNINGS AND PRECAUTIONS

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

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

• Active pathologically bleeding
• Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

Increased Risk of Thrombotic Events After Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

• Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  – Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRI, SNRI, and NSAIDs.
  – Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  – There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.

• Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the administration of ELIQUIS. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

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

• Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

• Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolyis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombosis or pulmonary embolectomy.

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

• Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., letrozol, latazol, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.

• Strong Dual Inducers of CYP3A4 and P-gp: Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

• Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolitics, heparin, aspirin, and chronic NSAIDs increase the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.
ELIQUIS is the #1 most prescribed oral anticoagulant among cardiologists for new patient starts*

Explore the efficacy and safety data

*Based on IMS SDI VECTOR New-to-brand Prescription Database (NBRx). Oral anticoagulant prescriptions were written by cardiologists and filled by patients who did not have any prescriptions filled for that same oral anticoagulant in the previous 6 months. Claims valid as of 1/3/14 to 8/12/16.

INDICATIONS
ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
ELIQUIS is indicated for the treatment of DVT and PE, and to reduce the risk of recurrent DVT and PE following initial therapy.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS
(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Please see additional Important Safety Information, including continued Boxed WARNINGS, on adjacent page.
Patients with Prosthetic Heart Valves

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

Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolytic Therapy

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

ADVERSE REACTIONS

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

- Increased risk of thrombotic events after premature discontinuation
- Bleeding [see Warnings and Precautions]

Clinical Trials Experience

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

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

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies (see Clinical Studies section). In the ARISTOTLE study, 11,360 patients with atrial fibrillation 65 years old or older were treated with ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was 12.5 months (3994 patients), 24 months (2999 patients), and 38 months (1932 patients) in the two studies. In ARISTOTLE, the mean duration of exposure was 96 hours (15,000 patient-years) in AVERROES, the mean duration of exposure was approximately 90 weeks (>3,000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions in patients treated with ELIQUIS. This occurred in 1.7% and 2.3% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% of ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

Bleeding during the treatment period is shown in Table 1.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>ELIQUIS (n=15,342)</th>
<th>Warfarin (n=15,013)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>347 (2.3%)</td>
<td>348 (3.1%)</td>
<td>0.73 (0.60, 0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9 (0.1%)</td>
<td>6 (0.0%)</td>
<td>0.71 (0.26, 2.02)</td>
<td>0.60</td>
</tr>
<tr>
<td>Intracranial (hemorrhage)</td>
<td>32 (0.2%)</td>
<td>15 (0.1%)</td>
<td>0.79 (0.57, 1.10)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intraspinal</td>
<td>3 (0.0%)</td>
<td>1 (0.0%)</td>
<td>0.83 (0.28, 2.72)</td>
<td>0.80</td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>3 (0.0%)</td>
<td>1 (0.0%)</td>
<td>0.83 (0.28, 2.72)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Bleeding in the subgroup analysis in Table 2.

Table 2: Major and Minor Bleeding Events in Patients Undergoing Elective Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ELIQUIS (n=12,500)</th>
<th>Warfarin (n=12,000)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75</td>
<td>275 (2.2%)</td>
<td>300 (2.5%)</td>
<td>0.84 (0.66, 1.10)</td>
<td>0.31</td>
</tr>
<tr>
<td>Male</td>
<td>339 (2.7%)</td>
<td>374 (3.1%)</td>
<td>0.86 (0.69, 1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>Evidence of prior bleeding history</td>
<td>154 (1.2%)</td>
<td>184 (1.5%)</td>
<td>0.83 (0.64, 1.08)</td>
<td>0.13</td>
</tr>
<tr>
<td>Spinal or epidural anesthesia</td>
<td>170 (1.4%)</td>
<td>196 (1.6%)</td>
<td>0.87 (0.67, 1.13)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Bleeding in the subgroup analysis in Table 3.

Table 3: Trends of Major and Minor Bleeding Events under ギイウジェン in Phase III Studies

<table>
<thead>
<tr>
<th>Bleeding Endpoints</th>
<th>ADVANCE-1 ARVT %</th>
<th>ADVANCE-2 ARVT %</th>
<th>ADVANCE-1 ARVT %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events (%)</strong></td>
<td><strong>Events (%)</strong></td>
<td><strong>Events (%)</strong></td>
<td><strong>Events (%)</strong></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-major bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: The table above presents effects in various subgroups, all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.
Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Condition</th>
<th>ELIQUIS (n=840)</th>
<th>placebo (n=811)</th>
<th>Relative Risk</th>
<th>p-Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>2.0 (0.2-17.8)</td>
<td>0.26 (0.05-1.1)</td>
</tr>
<tr>
<td>CRNM*</td>
<td>25 (3.0)</td>
<td>34 (4.2)</td>
<td>0.7 (0.1-4.2)</td>
<td>0.59 (0.22-1.5)</td>
</tr>
<tr>
<td>Minor</td>
<td>27 (3.2)</td>
<td>35 (4.3)</td>
<td>0.6 (0.2-2.0)</td>
<td>0.42 (0.18-0.97)</td>
</tr>
<tr>
<td>All</td>
<td>75 (9.0)</td>
<td>92 (11.9)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.25 (0.11-0.56)</td>
</tr>
</tbody>
</table>

* CRNM = clinically relevant nonmajor bleeding.

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

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 5.

Table 5: Bleeding Results in the AMPLIFY-EXT Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>ELIQUIS (n=840)</th>
<th>placebo (n=811)</th>
<th>Relative Risk</th>
<th>p-Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>2.0 (0.2-17.8)</td>
<td>0.26 (0.05-1.1)</td>
</tr>
<tr>
<td>CRNM*</td>
<td>25 (3.0)</td>
<td>34 (4.2)</td>
<td>0.7 (0.1-4.2)</td>
<td>0.59 (0.22-1.5)</td>
</tr>
<tr>
<td>Minor</td>
<td>27 (3.2)</td>
<td>35 (4.3)</td>
<td>0.6 (0.2-2.0)</td>
<td>0.42 (0.18-0.97)</td>
</tr>
<tr>
<td>All</td>
<td>75 (9.0)</td>
<td>92 (11.9)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.25 (0.11-0.56)</td>
</tr>
</tbody>
</table>

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose). Women should be instructed either to discontinue breastfeeding or to discontinue apixaban therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.


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

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

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD). In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose [see Dosage and Administration (2.1) in full Prescribing Information] may result in concentration of apixaban and pharmacodynamic activity similar to those observed in the AMPLIFY study [see Clinical Pharmacology (12.3) in full Prescribing Information]. This finding does not influence the dosing in patients with ESRD on dialysis as was seen in the AMPLIFY Study.

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

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

Clinical efficacy and safety studies with ELIQUIS did not enroll patients on dialysis or patients with a CrCl ≤1.5 mL/min. Therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic activity with apixaban in patients with ESRD on dialysis [see Clinical Pharmacology (12.3) in full Prescribing Information]. ELIQUIS is not recommended in patients with severe hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of apixaban increases the risk of bleeding [see Warnings and Precautions (5.1)].

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

In healthy subjects, administration of activated charcoal 2 to 6 hours after ingestion of a 25 mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily while on ELIQUIS.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other products that can affect blood pressure or bleeding
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations (8.1)]

- If any of these symptoms occur, advise the patient to seek emergent medical attention.
- At least three of the following:

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

- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas [see Warnings and Precautions (5.1)].
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS [see Use in Specific Populations (8.1)].
- If they have renal impairment, advise them to continue taking apixaban, provided they are not at risk of bleeding or at higher risk of bleeding.
- If they have a history of or are at risk of bleeding, advise them to continue taking apixaban, provided they are not at risk of bleeding or at higher risk of bleeding.

Marketed by Bristol-Myers Squibb Company

References

For treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE.

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

Clinical efficacy and safety studies with ELIQUIS did not enroll patients on dialysis or patients with a CrCl ≤1.5 mL/min. Therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic activity with apixaban in patients with ESRD on dialysis [see Clinical Pharmacology (12.3) in full Prescribing Information]. ELIQUIS is not recommended in patients with severe hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].
Most lung recipients gain 2-year survival benefit

BY BIANCA NOGRADY
PrimeMed Medical News

Early three-quarters of lung transplant recipients are likely to gain at least 2 years of survival, according to new research.

In a study published in the February issue of the Annals of the American Thoracic Society, researchers used data from 13,040 adults listed for lung transplantation between May 2003 and September 2011 to develop a structural nested accelerated failure time model of the survival benefit of lung transplantation over time.

“A structural nested model is used to compare the distribution of counterfactual residual survival if a patient were to receive a transplanted organ with the survival distribution if the patient did not receive that organ and never received one subsequently,” wrote David M. Vock, PhD, from the University of Minnesota, Minneapolis, and coauthors.

Using this approach, they calculated that 73.8% of transplant recipients were predicted to achieve a 2-year survival benefit with transplantation. At 1 year post transplantation, the relative survival benefit was 1.59, at 2 years it was 1.93, and at 3 years it was 2.23 (Ann Am Thorac Soc. 2017;14:172-81. doi: 10.1513/AnnalsATS.201606-507OC).

Patients’ lung allocation score at transplantation (LAS-T) – the score used to prioritize donated lungs for transplantation – had a significant impact on the survival benefit from transplantation. The relative survival benefit of transplantation increased by 59.4% as the lung allocation score increased from 30 to 35, and increased by 45.1% as the lung allocation score increased from 30 to 55.

However patients with a lung allocation score of 32.5 or less were more likely to die with a transplant than without, even over the long term, while patients with a score of 35 or more always gained a survival advantage from transplantation, even if their scores were as high as 50-100. The authors said this showed there should be no upper limit for the lung allocation score.

“It has been suggested that the LAS system may encourage patients who have clinically deteriorated to undergo transplantation even though it would be futile,” they wrote. “Our results reinforce the notion that lung transplantation should be considered an appropriate treatment option for patients with most advanced lung diseases and is expected to confer survival benefit in appropriately selected patients.”

Researchers also observed an interesting, borderline significant association between disease group and survival benefit, with individuals with obstructive lung disease showing the lowest relative survival gains and those with cystic fibrosis showing the highest. Head to head, the relative survival benefit of transplantation for those with cystic fibrosis was 54.4% greater than for those with obstructive lung disease.

Other factors such as transplant type, age, smoking, and center volume also influenced relative survival benefit. Bilateral transplants were associated with a 13.4% greater relative survival benefit, lungs from donors aged under 55 years showed a 17.9% relative survival benefit, and lungs from donors without a history of smoking showed a 10.5% increase in relative survival benefit.

However the researchers noted that their modeling focused on only the survival benefit of transplantation and did not take into account improvements in quality of life. This was likely to be particularly relevant in conditions such as chronic obstructive pulmonary disease where the quality of life benefits might justify transplantation even in the absence of a clear survival benefit.

“A comprehensive understanding of the survival benefit of lung transplantation and how that benefit varies by recipient characteristics is imperative to inform recipient selection, to justify the intensive health care resources allocated to this treatment, and to achieve an equitable allocation of donor lungs,” the researchers said.

The study was supported by the National Heart, Lung, and Blood Institute; the National Cancer Institute; and the National Institute of Allergy and Infectious Diseases. One author declared grants and personal fees from private industry for consultation on lung transplantation. No other conflicts of interest were declared.

Continued from page 13

malignancy, mesh erosion, and complications from extended intubation. Three patients had previous radiation therapy to the neck or chest. Five patients had defects localized to the membranous tracheal wall, two had defects of the mainstem bronchus or bronchus intermedius, and one patient had a defect of the anterior wall of the trachea.

Dr. Udelsman and coauthors used both aortic homograft and acellular dermal matrix to repair large defects. Their experience confirmed previous reports of the formation of granulation tissue with aortic autografts, underscoring the importance of frequent bronchoscopy and debridement when necessary. And while previous reports have claimed human acellular dermis resists granulation formation, that wasn’t the case in this study. “The exact histologic basis of bioprosthetic incorporation and reepithelialization in these patients is still elusive and will require further study,” Dr. Udelsman and coauthors said.

This study also employed the controversial muscle buttress repair in six patients, which helped, at least theoretically, to secure the repairs when leaks occur, to separate suture lines when both the airway and esophagus were repaired, and to support the bioprosthetic material to prevent tissue softening. Dr. Udelsman and coauthors said.

Postoperative examinations confirmed that the operations successfully closed the airway defects in all eight patients. Long term, most resumed oral intake, but three did not for various reasons: One had a paryngostomy; another had neurocognitive issues preoperatively; and a third with a tracheoesophageal fistula repair and cervical esphagosotomy could resume oral intake but depended on tube feeds to meet caloric needs.

All patients developed granulation at the repair site, two of whom required further debridement and one who underwent balloon dilation. Pneumonia was the most common complication within 30 days of surgery, occurring in two patients. Three patients died within 120 days from metastatic disease, and a fourth patient progressed to end-stage AIDS 6 years after the operation and eventually died.

Dr. Udelsman and coauthors reported having no financial disclosures.

Lung transplantation prolongs survival

Lung transplantation is the only option available for patients with treatment-resistant end-stage lung disease. However, the ability of this intervention to extend survival is still actively debated. The authors demonstrate that most adults undergoing lung transplantation experience a survival benefit that is mainly driven by the value of the lung allocation score at the time of transplantation and by the underlying lung disease.

It is reassuring to see that the two studies published so far that accounted for the course of patient disease after placement on a wait list reached essentially the same conclusions: Most of the patients experienced a survival benefit from lung transplantation.

Gabriel Thubut, MD, is from the service de pneumologie B and transplantation pulmonaire at the University of Paris. These comments are taken from an accompanying editorial (Ann Am Thorac Soc. 2017;14:163-4. doi: 10.1513/AnnalsATS.201611-833ED). No conflicts of interest were declared.

G. Hossein Almassi, MD, FCCP, comments:
This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:
This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:
This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:
This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:
This is a small series of 8 patients out of 342 total patients requiring airway repair who underwent repair of complicated major airway defects at a well-known tertiary referral center for airway surgery. The message is clear that complicated airway defects, as defined by the authors, should be referred to a high-volume specialty center with expertise in this field.
HOUSTON – About 1 in 10 Medicare patients require implantation of a permanent pacemaker after transcatheter aortic valve replacement, results from a large analysis showed.

“There is conflicting evidence and some debate over permanent pacemaker placement following transcatheter aortic valve replacement – whether it has a protective or adverse effect, and how often it takes place,” study investigator Fenton H. McCarthy, MD, said in an interview at the annual meeting of the Society of Thoracic Surgeons.

To evaluate the relationship between permanent pacemaker implantation and long-term patient outcomes among Medicare beneficiaries undergoing TAVR, Dr. McCarthy, a cardiothoracic surgery fellow at the University of Pennsylvania, Philadelphia, and his associates used Medicare carrier claims and Medicare Provider Analysis and Review files to identify 14,305 TAVR patients between January 2011 and December 2013.

The mean age of the 14,305 TAVR patients studied was 83 years, and 11% received a permanent pacemaker after TAVR. Of these, 9% received the pacemaker at index hospitalization, 1% at 30 days after implant, 0.5% at 90 days after implant, and 1% at 1 year after implant. Patient age of greater than 90 years was a significant predictor of pacemaker placement, with an odds ratio of 1.7 (P < 0.01).

Dr. McCarthy and his associates observed that the readmission rates for pacemaker placement and no pacemaker placement at index hospitalization were similar at 30 days (21% vs. 19%, respectively), at 90 days (33% vs. 31%) and at 1 year (43% in both groups of patients).

“After TAVR. Of these, 9% received a permanent pacemaker placement following TAVR. By Doug Brunk

**VIEW ON THE NEWS**

G. Hossein Almassi, MD, FCCP, comments: The need for new permanent pacemaker implantation in TAVR patients has been higher as compared with surgical AVR. The current analysis on the administrative database of Medicare patients undergoing TAVR has the advantage of a large sample size but lacks details at the patient level. The PARTNER 2A trial in medium-risk patients (N Engl J Med. 2016;374:1609-20) found no statistical difference between TAVR and surgical AVR for the need for permanent pacemaker implantation at 30 days (8.3% and 6.9%, respectively; P = 0.17).
Maintain conjugate vaccine schedule with preemies

BY DAN WATSON
Frontline Medical News

There should be no hesitation in administering the routine vaccination schedule for 13-valent pneumococcal conjugate vaccine (PCV13) on account of gestational age or birth weight in preterm infants, researchers concluded. In a phase IV study, researchers compared 100 term with 100 preterm infants; both groups were vaccinated on the routine schedule at ages 2, 3, 4, and 12 months. After the 12-month (toddler) dose of the PCV13, the infants were evaluated for serum antibody persistence at 12 and 24 months. “To date, no studies have examined the long-term persistence of immune responses to PCV13 in formerly preterm infants,” noted Federico Martín-Torres, MD, PhD, of Hospital Clínico Universitario de...
Santiago de Compostela, Spain, and his coauthors.

In the study, at six sites in Spain and five sites in Poland between October 2010 and January 2014, both groups were checked for geometric mean concentrations (GMC) of serotype-specific capsular immunoglobulin G–binding antibodies and for opsonophagocytic activity. All 200 subjects were white and were generally healthy; the preterm infants were grouped by gestational age at birth of less than 29 weeks (n = 25), 29 weeks to less than 32 weeks (n = 50), or 32 weeks to less than 37 weeks (n = 25). Twelve subjects dropped out of the study by the first year’s evaluation, and another eight of the term subjects and seven of preterm subjects dropped out by the second year’s evaluation (Ped Infect Dis J. 2017. doi: 10.1097/INF.0000000000001428).

At both follow-up time points, no discernible patterns were observed in IgG GMCs for any serotype or in opsonophagocytic activity geometric mean titers across preterm subgroups based on gestational age.

“The vaccination phase of the study demonstrated that preterm infants are able to generate an immune response to PCV13 that is likely to

Continued on page 25
Shunts often fail rapidly in neonates and infants

BY DOUG BRUNK
Pioneer Medical News

HOUSTON – Among neonates and infants who underwent shunt construction as a source of pulmonary blood flow, early, in-hospital shunt failure occurred in 7.3% of cases, resulting from a large retrospective study conducted on 22 patients who experienced cardiac surgery in the first year of life underwent construction of a systemic to pulmonary artery shunt of some type, one of the study investigators, Marshall L. Jacobs, MD, said in an interview. The study was presented at the annual meeting of the Society of Thoracic Surgeons.

“Early failure of such shunts is an incompletely understood phenomenon which accounts for important morbidity and mortality among infants who underwent shunt construction of some kind,” said Dr. Jacobs.

SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol, for oral inhalation use

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT® is indicated for the treatment of asthma in patients 6 years of age and older. LABA, as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether the increased risk of asthma-related death from LABA is neutralized by concomitant use of inhaled corticosteroids. The initiation of SYMBICORT in this setting is not appropriate. Unlike other LABA, formoterol is not designed to relieve acute symptoms such as shortness of breath. The use of SYMBICORT is contraindicated in the following conditions:

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

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.
- Hyperreactivity to any of the ingredients in SYMBICORT.
- SYMBICORT is NOT indicated for the relief of acute bronchospasm.
- SYMBICORT is NOT indicated for the relief of acute asthma.

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.
- Hyperreactivity to any of the ingredients in SYMBICORT.

Warnings and Precautions

Asthma-Related Death

LABA, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether the increased risk of asthma-related death from LABA is neutralized by concomitant use of inhaled corticosteroids. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related death 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 inhaled corticosterol. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids (see Warnings and Precautions (5.1)).

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

As with any other LABA containing beta₂-agonist, SYMBICORT should not be used more than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-related bronchospasm (ERB) 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 rarely in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Pneumonia and Other Lower Respiratory Tract Infections

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 severe 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 caution 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 high 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, randomized controlled 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=43) (i.e., beta-agonists, leukotriene receptor antagonists, or montelukast). The percentage of patients developing a seroprotective antibody titer of ≥1:5 (geometric serum antibody) 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.

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically administered 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 gastrointestinal) or other conditions associated with severe stress. 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 supplemental 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 dose by 10% to 20% every 4 days.
fants and neonates. Much of what is known about shunt failure is based on experiences reported from individual institutions. The few multicenter studies to date have been clinical trials that focused primarily on pharmacologic strategies intended to reduce the risk of shunt failure due to thrombosis. Their utility for guiding clinical decision making has been limited. Some have been underpowered; some have had limited risk adjustment of subjects. The current investigation, which began when Nhue Do, MD, was a cardiac surgery chief resident at John Hopkins Hospital, Baltimore, is the largest reported analysis of factors associated with postoperative in-hospital shunt failure in neonates and infants with congenital heart disease. It is the first multicenter study to define preoperative risk factors and patient characteristics associated with early shunt failure.

Dr. Do, who lead the find—Continued on following page
Norwood procedure) than with the
Endocrine disorders:
fibrillation, extrasystoles, palpitations
Cardiac disorders:
possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 1  Adverse reactions occurring at an incidence of
Nasopharyngitis 7.3 3.3 5.8 4.9
Sinusitis 5.8 4.8 2.5 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 1.1 0.6
Urticaria 3.2 2.4 3.7 3.0 1.3 0.6
Oral C Candidiasis 1.4 3.2 0.0 0.6 0.0 0.0
Ave Duration 77.7 73.8 77.9 71.4 62.4 56.9

Table 2  Adverse reactions occurring at an incidence of
Nasopharyngitis 7.3 3.3 5.8 4.9
Sinusitis 5.8 4.8 2.5 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 1.1 0.6
Urticaria 3.2 2.4 3.7 3.0 1.3 0.6
Oral C Candidiasis 1.4 3.2 0.0 0.6 0.0 0.0
Ave Duration 77.7 73.8 77.9 71.4 62.4 56.9

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

Long-term safety - asthma clinical trials in pediatric patients

The incidence of adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (12 and 13 months in duration) in which 771 asthmatic children aged 6 to 11 years of age were treated with SYMBICORT 160/4.5, 2 inhalations twice daily. Of these 761 patients who were enrolled for 6 months and were treated for 12 months, The SYMBICORT group was composed of mostly Caucasian (65%) patients with a mean age of 6.9 years, and a mean weight of 41 kg. At baseline, 33%, Control arms for comparison included 2 inhalations of budesonide HFA (MDI), 160 mcg, formoterol 4.5 mcg or placebo (MDI/EPF). 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.

Beta-Adrenergic Receptor Blocking Agents

Meta-analysis of asthma data from SYMBICORT clinical trials showed that asthma patients treated with SYMBICORT had a significantly lower weight than patients treated with placebo. The incidence of common adverse events in Table 2 below is based upon pooled data from 3 asthma clinical trials in patients 12 years and older. The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks of treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT or placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled studies. The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks of treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT or placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled studies.

Student's t-tests were conducted within-stratum to determine the significance of differences. No formal drug interaction studies have been performed with SYMBICORT.

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 increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

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 increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, but may also produce 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, combination therapy would be considered, although they should be administered with caution.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.

The potential for acute toxic effects following overdose of budesonide is low. Budesonide is a racemic mixture of the alpha and beta isomers. The active moiety is the beta isomer which is thought to be 85% active in comparison to the alpha isomer. Budesonide is metabolized in the liver to a number of metabolites which are rapidly excreted via the kidneys. Budesonide is not known to cause significant toxicity at therapeutic levels.
Double-dose influenza vaccine gives best protection

BY DEEPAK CHITNIS
Frontline Medical News

A double-dose inactivated quadrivalent influenza vaccine (IV4) could be administered to all children aged 6-35 months, as it not only offers the best protection against influenza type B but also allows for simplifying the current vaccination schedule considerably.

“The introduction of IV4 provides an opportunity to review long-accepted practices in administration of influenza vaccines,” explained Varsha Jain, MD, formerly employed by GlaxoSmithKline Vaccines, King of Prussia, Pa., and associates.

“If the double-dose vaccine could be administered in young children without adverse effects on tolerability, this age group may benefit from potentially improved immunogenicity,” they wrote.

Giving a lower dose to young children was planned to reduce reactogenicity and febrile convulsions observed with the whole virus vaccines that were in use in the 1970s. But young children have a variable immune response to lower doses, especially against vaccine B strains, they noted (J Ped Infect Dis. 2017 Jan 6. doi: 10.1093/jpids/piw068).

Dr. Jain and coauthors enrolled 2,430 children aged 6-33 months during the 2014-2015 influenza season in the United States and Mexico in this phase III study. Children were randomized into one of two cohorts: one cohort received a standard-dose IV4 vaccination, while the other received a double dose. Data on age (6-17 months, 18-35 months), health care center, and influenza primer status also were taken into consideration.

The standard-dose vaccine contained 7.5 mcg of A/Cali-fornia/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Bris-bane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata), while the double-dose vaccine contained 15 mcg, or twice the amount each, of the same strains. The former was developed by Sanofi Pasteur and the latter by GSK Vaccines.

Primed children who completed the study numbered 1,173; 586 received the standard dose and 587 received the double dose. On the unprimed side, 868 completed the study: 442 standard dose and 426 double dose. Each dose’s immunogenicity was quantified by calculating the geometric mean titer (GMT) ratio.

“Immunogenicity was higher in the double-dose group compared with the standard-dose group, particularly against vaccine B strains in children 6-17 months of age and unprimed children,” Dr. Vain and associates said.

Both vaccines performed well against the influenza B strain, with the double dose yielding a GMT of 1.89 against the B/Yamagata strain and 2.13 against the B/Victoria in children aged 6-17 months. Across the entire age spectrum of the study population, unprimed children registered a GMT of 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

“Increased protection against influenza B would be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity,” the authors concluded. “This study provides evidence to support a change in clinical practice to use [double-dose IV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved.”

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.

Bromchiolitis pathway adherence tied to reduced LOS, costs

BY LORI LAUBACH
Frontline Medical News

High adherence to bronchiolitis clinical pathway recommendations in health care settings is associated with shorter length of stay (LOS) and lower health care costs, according to Mersine A. Bryan, MD, of the University of Washington, Seattle and her associates.

In a retrospective cohort study, researchers looked at 267 patients less than 24 months old diagnosed with bronchiolitis from December 2009 to July 2012. Levels of adherence were then categorized into low, middle, and high tertiles. Results show that adherence was highest for the inpatient quality measure scores in the highest tertile, compared with the lowest tertile, they said.

The mean ED LOS for cases with ED adherence scores in the highest tertile was 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

“Increased protection against influenza B would be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity,” the authors concluded. “This study provides evidence to support a change in clinical practice to use [double-dose IV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved.”

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.

Continued from page 21

Bromchiolitis pathway adherence tied to reduced LOS, costs

BY LORI LAUBACH
Frontline Medical News

High adherence to bronchiolitis clinical pathway recommendations in health care settings is associated with shorter length of stay (LOS) and lower health care costs, according to Mersine A. Bryan, MD, of the University of Washington, Seattle and her associates.

In a retrospective cohort study, researchers looked at 267 patients less than 24 months old diagnosed with bronchiolitis from December 2009 to July 2012. Levels of adherence were then categorized into low, middle, and high tertiles. Results show that adherence was highest for the inpatient quality measure scores in the highest tertile, compared with the lowest tertile, they said.

The mean ED LOS for cases with ED adherence scores in the highest tertile was 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

“Increased protection against influenza B would be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity,” the authors concluded. “This study provides evidence to support a change in clinical practice to use [double-dose IV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved.”

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.

Continued from page 21

Bromchiolitis pathway adherence tied to reduced LOS, costs

BY LORI LAUBACH
Frontline Medical News

High adherence to bronchiolitis clinical pathway recommendations in health care settings is associated with shorter length of stay (LOS) and lower health care costs, according to Mersine A. Bryan, MD, of the University of Washington, Seattle and her associates.

In a retrospective cohort study, researchers looked at 267 patients less than 24 months old diagnosed with bronchiolitis from December 2009 to July 2012. Levels of adherence were then categorized into low, middle, and high tertiles. Results show that adherence was highest for the inpatient quality measure scores in the highest tertile, compared with the lowest tertile, they said.

The mean ED LOS for cases with ED adherence scores in the highest tertile was 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

“Increased protection against influenza B would be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity,” the authors concluded. “This study provides evidence to support a change in clinical practice to use [double-dose IV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved.”

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.

Continued from page 21

Bromchiolitis pathway adherence tied to reduced LOS, costs

BY LORI LAUBACH
Frontline Medical News

High adherence to bronchiolitis clinical pathway recommendations in health care settings is associated with shorter length of stay (LOS) and lower health care costs, according to Mersine A. Bryan, MD, of the University of Washington, Seattle and her associates.

In a retrospective cohort study, researchers looked at 267 patients less than 24 months old diagnosed with bronchiolitis from December 2009 to July 2012. Levels of adherence were then categorized into low, middle, and high tertiles. Results show that adherence was highest for the inpatient quality measure scores in the highest tertile, compared with the lowest tertile, they said.

The mean ED LOS for cases with ED adherence scores in the highest tertile was 1.85 and 2.04 against the same strains, respectively. For comparison, none of the A strains in any cohort based on age or primed/unprimed registered a GMT above 1.5.

“Increased protection against influenza B would be a beneficial clinical outcome [and] use of the same vaccine dose for all eligible ages would also simplify the annual influenza vaccine campaign and reduce cost and logistic complexity,” the authors concluded. “This study provides evidence to support a change in clinical practice to use [double-dose IV4] in all children 6 months of age and older, once that dosing for a vaccine product has been approved.”

Dr. Jain now is employed by the Bill and Melinda Gates Foundation. Dr. Jain and several coauthors disclosed ties to GlaxoSmithKline, which funded the study.
48% of pediatric HA-VRIs caused by rhinovirus

BY KATIE WAGNER LENNON
Frontline Medical News

Health care–associated viral respiratory infections (HA-VRIs) were common in two pediatric hospitals, with rhinovirus the most frequent cause of the infections in a 3-year analysis.

The incidence rate of laboratory-confirmed HA-VRIs was 1.29/1,000 patient-days in an examination of the hospitals’ patient data. Forty-eight percent of all 323 HA-VRI cases were caused by rhinovirus, with an overall incidence rate of 0.72/1,000 patient-days. Additionally, rhinovirus was the most frequently identified virus in cases of HA-VRI in almost all units of both hospitals, followed by parainfluenza virus and respiratory syncytial virus. The exception was the medical/surgical ward of Steven and Alexandra Cohen Children’s Medical Center (CCMC) of New York; in this unit of the CCMC, the incidence rate of parainfluenza virus was higher than that of rhinovirus (0.21/1,000 patient-days vs. 0.15/1,000 patient-days) (J Ped Inf Dis. 2016. doi: 10.1093/pjids/piw072).

The researchers used infection prevention and control surveillance databases from Montreal Children’s Hospital and the CCMC to identify HA-VRIs that occurred between April 1, 2010, and March 31, 2013. In both hospitals, HA-VRIs were attributed to the unit to which the patient was admitted at the time of transmission. Both hospitals used a multiplex nucleic acid amplification test for respiratory virus detection on nasopharyngeal swabs or aspirates.

“An HA-VRI with an onset of symptoms after hospital discharge would be detected and included only for patients who presented to the emergency department or were readmitted for VRI and tested,” according to Caroline Quach, MD, of the Montreal Children’s Hospital, McGill University Health Centre, and her colleagues.

The HA-VRI rate was 1.91/1,000 patient-days at Montreal Children’s Hospital, compared with 0.80/1,000 patient-days at the CCMC (P less than .0001). At the CCMC, the HA-VRI incidence rate was lowest in the neonatal ICU, but at Montreal Children’s Hospital, the hematology/oncology ward had the lowest rate of HA-VRI.

Having less than 50% single rooms in a given unit was associated with a statistically significantly higher rate of HA-VRI, after the investigators adjusted for unit type and took the correlation of HA-VRI rates within a hospital into consideration. The study authors’ model predicted that units with less than 50% single rooms have 1.33 times higher HA-VRI rates than units with at least 50% single rooms, regardless of unit type.

Dr. Quach has received funding from GlaxoSmithKline, Pfizer, Sage, and AbbVie for an unrelated research project, while the other authors disclosed no financial relationships.

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

![Diagram of the 3 key pathways](image)

**ENDOTHELIN PATHWAY**

**NITRIC OXIDE PATHWAY**

**PROSTACYCLIN PATHWAY**

**GRIphon: The First PAH Outcomes Trial That Included Patients Treated With Triple-Combination Therapy**

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

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

**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

Pulmonary Veno-Occlusive Disease (PVOD)

**ADVERSE REACTIONS**

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

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

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

**DRUG INTERACTIONS**

**Strong CYP2C8 inhibitors**

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

*UPTRAVI in combination with an ERA and PDE-5i.*
RSV is preemies’ top severe respiratory disease source

BY BIANCA NOGRADY
Frontline Medical News

Respiratory syncytial virus is the number one virus causing severe lower respiratory disease in preterm infants, while those of younger age and those exposed to young children are at greatest risk, Eric A. F. Simões, MD, of the University of Colorado at Denver, Aurora, and his coauthors reported in the Nov. 29 edition of PLOS ONE. “These data demonstrate that higher risk for 32 to 35 wGA [weeks gestational age] infants can be easily identified by age or birth month and significant exposure to other young children,” they wrote. “These infants would benefit from targeted efforts to prevent severe RSV disease.”

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

A primary endpoint event was experienced by 27.0% (155/574) of UPTRAVI-treated patients vs 41.6% (242/582) of placebo-treated patients. Disease progression primary endpoint comprised the following components as first events (up to end of treatment; UPTRAVI vs placebo):

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

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

IMPORTANT SAFETY INFORMATION (cont’d)

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

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

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

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


Visit www.UPTRAVI.com/hcp to learn more
Infants born in May, before the RSV season, had much lower rates of hospitalization and ICU admission, compared with infants born at the height of RSV season in February. RSV: The incidence ranged from 8.2 per 100 infant-seasons in those aged less than 1 month to 2.3 per 100 infant-seasons in those aged 10 months of age. Similarly, the incidence of admission to ICU was significantly higher among younger infants.

Infants born in May, before the RSV season, had a much lower incidence of hospitalization, compared with those born in the height of RSV season in February. ICU admission rates also were higher among those born in February, compared with those born in May.

The highest overall rates of hospitalization with RSV – 19 per 100 infant-seasons – were among those born in February, and also those who were exposed to other young children.

“The current results are unique in that they provide continuous age-based risk models for infants and infantile disease for infants and with young child exposure,” wrote Dr. Simões and his colleagues.

The study was supported by AstraZeneca, parent company of MedImmune. Two authors declared grant support and research funding from AstraZeneca, one author was a former employee of AstraZeneca, and one author was a former employee of MedImmune and now contractor to AstraZeneca. One author was a current employee of AstraZeneca and holds stock options. Two authors also declared funding and consultations with AbbVie.
NEW ORLEANS – Thromboprophylaxis for 35-42 days with the new oral anticoagulant betrixaban led to a significant reduction in all-cause and ischemic strokes in medically ill patients who required hospitalization as compared with conventional prophylaxis for 10 days, based on a post-hoc analysis of data from a randomized trial with more than 7,300 patients.

But the trial’s unusual design left it unclear whether the incremental benefit seen from prolonged prophylaxis with a NOAC resulted primarily from a longer period of treatment, the drug used, or both.

The Kaplan-Meier analysis showed that stroke incidence in the two intervention arms began to diverge during the first 10 days when all patients received an anticoagulant, suggesting that betrixaban surpassed enoxaparin when the two therapies went head to head, C. Michael Gibson, MD, said at the American Heart Association scientific sessions. Beyond the first 10 days and out to 77 days of follow up – during the period when standard enoxaparin prophylaxis in the control patients had ended but the novel regimen with betrixaban continued – the curve of strokes in the betrixaban group continued to separate sharply from that of the control group, indicating extended prophylaxis offered substantial benefit, said Dr. Gibson, a professor of medicine at Harvard Medical School and an interventional cardiologist at Beth Israel Deaconess Medical Center, both in Boston.

The safety analysis showed that prolonged treatment with betrixaban roughly doubled the rate of major or clinically relevant nonmajor bleeding events during the period of treatment and for the first 7 days after treatment stopped. The incidence of these bleeds was 1.6% among control patients on 10 days of enoxaparin treatment and 3.1% among patients who received extended treatment with betrixaban, a statistically significant difference. The rates of fatal bleeds and intracranial hemorrhages in the two study groups did not significantly differ.

The data Dr. Gibson reported came from the Multicenter, Randomized, Active-Controlled Efficacy and Safety Study Comparing Extended Duration Betrixaban With Standard of Care Enoxaparin for the Prevention of Venous Thromboembolism in Acute Medically Ill Patients (APEX). The study’s primary aim was testing in 7,513 hospitalized medically ill patients the safety and efficacy of extended-duration betrixaban, compared with 10 days of prolonged prophylaxis with the oral, factor Xa inhibitor betrixaban, Portola, submitted an application to the US Food and Drug Administration to approve marketing of extended-duration betrixaban for VTE prophylaxis in acute medically ill patients with VTE risk factors. In December 2016, Portola announced that the FDA had given the application priority status for a decision.

The post-hoc analysis that Dr. Gibson presented at the meeting looked at the impact of betrixaban compared with enoxaparin on the incidence of all-cause and ischemic stroke during 77 days of follow-up after the start of treatment in the 7,432 patients who received at least one dose of their assigned drug, two endpoints that weren’t even secondary outcomes in APEX’s original design.

Among the 3,716 treated with betrixaban, the all-cause stroke incidence was 0.54%; among the 3,716 patients treated with enoxaparin, the all-cause stroke incidence was 0.97%. The 56% relative risk reduction was statistically significant. The incidence of ischemic strokes was 0.48% with betrixaban and 0.91% with enoxaparin, a 53% relative risk reduction that was also statistically significant.

The post-hoc analysis also looked specifically at the comparison between betrixaban and enoxaparin for stroke prevention in a subgroup of patients who had the highest stroke rate, the patients who were hospitalized because of an index stroke or an index heart failure episode. In this high-risk subgroup, prophylaxis with betrixaban cut the all-cause stroke rate compared with enoxaparin by 49% and the ischemic stroke rate by 45%, both statistically significant effects.

Dr. Gibson has been a consultant to Eli Lilly, The Medicines Company, Novo Nordisk, Pfizer, and St. Jude. He has received research support from Portola and several other companies.

mzoler@frontlinemedcom.com
On Twitter @mitchelzoler

Extended-duration thromboprophylaxis may help

The APEX study identified a group of patients hospitalized for medical reasons who were at high risk for both venous thromboembolism and for stroke. We are comfortable with the concept of thromboprophylaxis for hospitalized patients who are at high risk for venous thromboembolism, but we have generally not paid attention to prophylaxis against stroke during and immediately after hospitalization.

The results suggest that extended thromboprophylaxis beyond the standard period of 10 days may be a good idea. Because patients in the two treatment arms of the study differed in both the drugs they received and in the duration of prophylaxis, the results cannot distinguish which of these two variables was more important. Treating patients with enoxaparin for 35-42 days may provide a similar benefit to what was seen with extended-duration betrixaban. Although daily treatment at home with injected enoxaparin is less convenient than outpatient treatment with an oral drug like betrixaban, extended-duration enoxaparin is a feasible option. The Kaplan-Meier curves that Dr. Gibson presented indicate that most of the incremental benefit from betrixaban occurred after 10 days, once it was compared with no prophylaxis at all in the control arm with short-duration enoxaparin.

The findings are a wake-up call to the high thromboembolic risk faced by the types of patients enrolled in APEX, and they point to a new way to manage these patients. Guidelines already call for putting high-risk patients, such as those with heart failure, on anticoagulant prophylaxis if they have no contraindications. These new data suggest that thromboprophylaxis in appropriate patients should extend beyond 10 days and beyond acute hospitalization.

Steven R. Lentz, MD, is a professor of medicine and a hematologist-oncologist at the University of Iowa in Iowa City. He has been a consultant to Novo Nordisk and Opko, has an ownership interest in Celgene, and has received research grants from Novo Nordisk. He made these comments in an interview.
Infections plummet with new catheter interventions

**BY ABIGAIL CRUZ**

Frontline Medical News

Q uality improvement (QI) interventions related to the use of central venous catheters (CVCs) were, on average, associated with 57% fewer infections and $1.85 million in net savings to hospitals within 1-3 years of implementation, based on the results of a meta-analysis of data from 113 hospitals. “Hospitals that have already attained very low infection rates (through the use of quality improvement checklists) would likely see smaller clinical benefits and savings than in the studies we have reviewed,” said Dr. Teryl Nuckols of Cedars-Sinai Medical Center, Los Angeles. “Nonetheless, we found that QI interventions can be associated with declines in CLABSI (central line-associated bloodstream infection) and/or CRBSI (catheter-related bloodstream infection) and net savings when checklists are already in use, and when hospitals have CLABSI rates as low as 1.7-3.7 per 1,000 CVC-days.”

Dr. Nuckols and colleagues did a literature search and examined results from 15 unique studies representing data from 113 acute care hospitals. All studies addressed quality improvement interventions designed to prevent CLABSI and/or CRBSI.

Studies were eligible for the analysis if they reported or estimated the quality improvement intervention’s clinical effectiveness, measured or modeled its costs, compared alternatives to the intervention, and reported both program and infection-related costs. Insertion checklists were examined in 12 studies, physician education in 11 studies, ultrasound-guided placement of catheters in 3 studies, all-inclusive catheter kits in 5 studies, sterile dressings in 5 studies, chlorhexidine gluconate sponge or antimicrobial dressing in 2 studies, and antimicrobial catheters in 2 studies.

Overall, the weighted mean incidence rate ratio was 0.43 (95% confidence interval, 0.35-0.51) and incremental net savings were $1.85 million (95% CI, $1.30 million to $2.40 million) per hospital over 3 years (2015 U.S. dollars). Each $100,000 increase in program cost was associated with $315,000 greater savings (95% CI, $166,000-$464,000; P less than .001). Infections and net costs declined when hospitals already used checklists or had baseline infection rates of 1.7-3.7 per 1,000 catheter-days (doi: 10.1001/jamainternmed.2016.6610).

Dr. Nuckols acknowledged that the price tag for achieving these savings “may be burdensome for hospitals with limited financial resources … wages and benefits account for two-thirds of all spending by hospitals, and a quarter of hospitals have had negative operating margins in recent years. We found that, for CLABSI- and CRBSI-prevention interventions, median program costs were about $270,000 per hospital over 3 years – but reached $500,000 to $750,000 in some studies.”

Hospitals that have already attained very low infection rates would likely see smaller clinical benefits than in the studies reviewed, noted Dr. Teryl Nuckols.

Moderate artery stenosis often becomes severe

**BY DOUG BRUNK**

Frontline Medical News

HOUSTON – Most nongrafted, moderately stenosed coronary arteries progress to severe stenosis or occlusion in the long term, results from a large, long-term study have shown. “Not uncommonly, patients referred for coronary surgery have one or more coronary arteries with only moderate stenosis,” Joseph F. Sabik III, MD, said at the annual meeting of the Society of Thoracic Surgeons. “There is controversy as to whether arteries with only moderate stenosis should be grafted during coronary surgery, and if it should be grafted, with what conduit?” For example, the Fractional Flow Reserve-Guided PCI Versus Medical Therapy in Stable Coronary Disease study, known as FAME, suggests not intervening on moderate stenosis, since stenting non–ischemia-producing lesions led to worse outcomes (N Engl J Med. 2012 Sep 13;367:991-1001). However, Dr. Sabik, who chairs the department of surgery at University Hospitals Cleveland Medical Center, and his associates recently reported that grafting moderately stenosed coronary arteries during surgical revascularization is not harmful and can be beneficial by improving survival if an internal thoracic artery graft is used (J Thoracic Cardiovasc Surg. 2016 Mar;151[3]:806-11).

In an effort to determine how grafting moderately stenosed coronary arteries influences native-vessel disease progression, and whether grafting may be protective from late ischemia, Dr. Sabik and his associates evaluated the medical records of 55,567 patients who underwent primary isolated coronary artery bypass graft (CABG) surgery at the Cleveland Clinic from 1972 to 2011. Of the 55,567 patients, 1,902 had a single coronary artery with angiographically moderate stenosis (defined as a narrowing of 50%-69%) and results of at least one postoperative angiogram available. Of these moderately stenosed coronary arteries (MSCAs), 488 were not grafted, 385 were internally thoracic artery (ITA)–grafted, and 1,028 were saphenous vein (SV)–grafted. At follow-up angiograms, information about disease progression was available for 488 nongrafted, 371 ITA-grafted, and 957 SV-grafted MSCAs, and patency information was available for 376 ITA and 1,016 SV grafts to these MSCAs. Grafts were considered patent if they were not occluded. Severe occlusion was defined as a narrowing of more than 70%.

The researchers found that at 1, 5, and 15 years, native-vessel disease progressed from moderate to severe stenosis/occlusion in 32%, 52%, 66%, and 72% of nongrafted MSCAs, respectively; in 55%, 73%, 84%, and 87% of ITA-grafted MSCAs, and in 67%, 82%, 90%, and 92% of SV-grafted MSCAs. After Dr. Sabik and his associates adjusted for patient characteristics, disease progression in MSCAs was significantly higher with ITA and SV grafting, compared with nongrafting (odds ratios, 3.6 and 9.9, respectively). At 1, 5, 10, and 15 years, occlusion in grafts to MSCAs was 8%, 9%, 11%, and 15%, respectively, for ITA grafts and 13%, 32%, 46%, and 56% for SV grafts. At these same time points, protection from myocardial ischemia in ITA-grafted vs. nongrafted MSCAs was 29%, 47%, 59%, and 61%.

“Our opinion is you that shouldn’t ignore moderate lesions,” Dr. Sabik, surgeon-in-chief and vice president for surgical operations for the University Hospitals system, said in an interview at the meeting. “Although it may not help that patient over the next short period of time, over their lifespan it will. What works for intervention doesn’t necessarily mean it’s right for bypass surgery.

If you have a vessel that’s only moderately stenosed you should at least consider grafting it, because moderate lesions progress over time. Bypassing it helps people live longer when you use an internal thoracic artery graft, because they are likely to remain patent. You always have to individualize the therapy, but the key is to use your grafts in the best way possible.”

Dr. Sabik disclosed that he has received research grants from Medtronic, Abbott Vascular, and Edwards Lifesciences.
CONSIDER MAKING 24-HOUR BREO YOUR GO-TO ICS/LABA OPTION

BREO 100/25 is for maintenance treatment of airflow obstruction in patients with COPD, and for reducing COPD exacerbations in patients with a history of exacerbations. BREO 100/25 is the only strength indicated for COPD.

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

BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information

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

BOXED WARNING CONTINUED ON NEXT PAGE

Please see additional Important Safety Information for BREO on pages 2–4.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.
In patients with asthma uncontrolled on an ICS

BREO 100/25 (n=312) provided a 108-mL improvement from baseline in weighted mean (wm) FEV₁ (0-24 hours) vs fluticasone furoate (FF) 100 mcg (n=288) at Week 12 (P<0.001).²

**Study description**

**Design:** 12-week, randomized, double-blind study that evaluated the safety and efficacy of BREO 100/25, BREO 200/25, and FF 100 mcg (each administered once daily in the evening). Patients who reported symptoms and/or rescue beta₂-agonist use during a 4-week run-in period on mid- to high-dose ICS (≥250 mcg fluticasone propionate [FP] twice daily or equivalent) were randomized to treatment.

**Patients:** 1039 patients with asthma aged 12 years and older †† (mean age: 46 years). At baseline, patients had a mean percent predicted FEV₁ of 62%.

†† BREO is approved for use in patients ≥18 years of age.

**Primary endpoint:** wm FEV₁ (0-24 hours) at Week 12.

Weighted mean FEV₁ (0-24 hours) was calculated from predose FEV₁ (within 30 minutes of dose) and postdose FEV₁ after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours.

FEV₁ = forced expiratory volume in 1 second; LS = least squares.

---

**Important Safety Information (cont’d)**

**WARNING: ASTHMA-RELATED DEATH (BOXED WARNING cont’d)**

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

**CONTRAINDICATIONS**

The use of BREO is contraindicated in the following conditions:

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

**WARNINGS AND PRECAUTIONS**

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with COPD

BREO 100/25 (n=33) provided a 220-mL improvement from baseline in 
wm FEV₁ (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (P<0.001). 3,4

Study description
Design: randomized, double-blind, crossover study compared the effect of 28 
days of treatment with BREO 100/25 and placebo (each administered once daily in the 
morning) on lung function over 24 hours.
Patients: 54 patients (mean age: 
58 years) with COPD who had a mean 
percent predicted postbronchodilator FEV₁, 
of 50% and a mean postbronchodilator 
FEV₁/FVC ratio of 53%.
Primary endpoint: 
wm FEV₁ (0-24 hours) 
at end of 28-day treatment period.
Secondary endpoint: 
Serial FEV₁ (0-24 hours) assessed 
over 1 full day at Days 28 and 29.


Please see additional Important Safety Information for BREO on 
pages 1, 2, and 4. 
Please see accompanying Brief Summary of Prescribing Information, 
including Boxed Warning, for BREO on pages 5–7.
Important Safety Information (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

• Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

• Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.

• Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.

• Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.

• Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflavin, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

• If paradoxical bronchospasm occurs, discontinue BREO and institute alternative therapy.

• Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.

• Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

• Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.

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

• Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

• Be alert to hypokalemia and hyperglycemia.

• Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

ADVERSE REACTIONS: BREO FOR COPD

• The most common adverse reactions (≥2% and more common than placebo) reported in two 6-month clinical trials with BREO (and placebo) were: nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).

• In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects with COPD treated with BREO in two 1-year studies included back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.
BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation BREO® ELLIPTA® 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation The following is a brief summary; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta–adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13/11,176 in subjects treated with salmeterol) vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO. Determine whether the rate of asthma-related death is increased in subjects treated with BREO has been conducted. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

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

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 no longer controls symptoms of bronchoconstriction; the patient’s inhaled, short-acting, beta–agonist use, be decreased as little as effective; or when the COPD exacerbation is considered severe, particularly when beta–agonist and corticosteroid therapy is considered. In this setting, the patient should be evaluated for the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation dose of BREO daily.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used. Symptoms should be treated with an inhaled, short-acting, beta–agonist, and systemic corticosteroids. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting, beta–agonist-only (on a regular basis, e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting, beta–agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta–Agonists: BREO should not be used more often than recommended, at higher doses than recommended, or in combination with another beta–agonist-containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another beta–agonist-containing LABA, salmeterol, formoterol fumarate, or inhaled corticosteroids for maintenance or even improvement of respiratory function.

5.4 Local Effects of ICS:

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

5.5 Pneumonia:

An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO 100/25 in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some instances these pneumonia events were fatal. Patients should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of persistent exacerbations of COPD. If a patient is suspected of pneumonia, chest X-ray should be performed.

In replicate 12-month trials in 2,355 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 3% (51 of 1650 subjects); and placebo: 2% (75 of 3,895 subjects) than in subjects receiving vilanterol 5 mcg: 3% (27 of 818 subjects). There was no fatal pneumonia in subjects receiving vilanterol furoate/vilanterol 25 mcg/50 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (less than 1% for each treatment group).

5.6 Immunosuppression:

Persons who use drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients treated with BREO. If reactivation of varicella-zoster virus (e.g., chickenpox or herpes zoster) occurs in a patient who is exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. (See the respective package inserts for complete VZIG and IS prescribing information.) If chickenpox develops, treatment with antiviral drugs may be considered.

BREO should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or other conditions. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, urticaria, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systematically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression:

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9). Drug Interactions (7.1)]. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for 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 with underlying disease and/or prior corticosteroid treatment. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:

Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,续下页
5.10 Paradoxical Bronchospasm: As with other inhaled medicines, BREO can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO should be discontinued immediately; and alternative therapy should be instituted.

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

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

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

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

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

5.15 Coexisting Conditions: BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta,-adrenergic antagonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketosis diabetes.

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

5.17 Effect on Growth: Daily inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. [See Use in Specific Populations (8.4) for full prescribing information.]

7 ADVERSE REACTIONS

LABA, such as vilteramer, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. [See Warnings and Precautions (5.5).]

Orally inhaled corticosteroids may cause a reduction in growth velocity and should be used to treat or prevent osteoporosis should be strongly considered. In general, serum and bone mineral density assessments with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient’s COPD therapy, use of medicine to treat or prevent osteoporosis should be considered.

5.21 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease: The clinical program for BREO included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 others that showed a reduction in asthma-related deaths in subjects receiving salmeterol. [See Warnings and Precautions (5.5).]

5.2.1 Clinical Trials: The incidence of adverse reactions associated with BREO 100/25 is based on 5 placebo-controlled, 6-month clinical trials (n=1,224 to n=1,063, respectively) have been associated with clinically significant prolongation of the QT interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

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

5.2.4 Reduction in Bone Mineral Density: Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fractures with vertebral compression fractures for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter. If significant reductions in BMD are seen and BREO is still considered medically important for that patient’s COPD therapy, use of medicine to treat or prevent osteoporosis should be considered.
for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

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

8 USE IN SPECIFIC POPULATIONS

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

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m² basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day).

Fluticasone Furoate: There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 23,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 551 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

Non-teratogenic Effects: Hypoadrenalinism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

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

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

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

In a 24- to 76-week exacerbation trial, subjects received BREO 100/25 (n=1,009) or fluticasone furoate 100 mcg (n=1,010). Subjects had a mean age of 42 years and a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. [See Clinical Studies (14.2) of full prescribing information.] Adolescents aged 12 to 17 years made up 14% of the study population (n=281), with a mean age of 17 years. Studies (14.2) of full prescribing information.

8.5 Geriatric Use: Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for COPD included 2,558 subjects aged 65 and older and 564 subjects aged 75 and older. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

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

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

10 OVERDOSAGE: No human overdose data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdose for the individual components described below apply equally to BREO. Treatment of overdose consists of standard supportive measures. No patient-specific supportive measures of BREO are known. Cardiac monitoring is recommended in cases of overdose.

10.1 Fluticasone Furoate: Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdose of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur [see Warnings and Precautions (5.17)]. Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

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

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

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

Not for Acute Symptoms: Inform patients that BREO is not intended to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta–agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

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

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

Do Not Use Additional Long-acting Beta–agonists: Instruct patients not to use other LABA for COPD and asthma.

Local Effects: Inform patients that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) anti fungal therapy while still continuing therapy with BREO, but at times therapy with BREO may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water after swallowing after inhalation to help reduce the risk of thrush.

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

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

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

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

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

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

Hypersensitivity Reactions, including Anaphylaxis: Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO.

Instruct patients to discontinue BREO if such reactions occur.

There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

BREO and ELLIPTA are registered trademarks of the GSK group of companies.

BREO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

©2016, the GSK group of companies. All rights reserved.

BREO/7BR

©2016 GSK group of companies. All rights reserved.

Printed in USA, 80463830 November 2016

©2016 GSK group of companies. All rights reserved.
Nailfold videocapillaroscopy can help to predict which patients with systemic sclerosis (SSc) may develop serious cardiopulmonary complications, according to findings from a Dutch cross-sectional study. While individual autoantibodies seen in systemic sclerosis (SSc) are known to be associated with greater or lesser risk of cardiopulmonary involvement, in this study nailfold vascularization patterns independently predicted pulmonary artery hypertension or interstitial lung disease.

For their research, Iris M. Markusse, MD, PhD, and her colleagues at Leiden (the Netherlands) University Medical Center collected data on nailfold videocapillaroscopy (NVC) patterns and SSc-specific autoantibodies from a cross section of 287 patients in an established SSc cohort (Rheumatology [Oxford]. 2016 Dec 10. doi: 10.1093/rheumatology/kew402).

All patients in the study had NVC pattern data as well as anti-extractable nuclear antigen (anti-ENA) antibodies. The mean age of the patients was 54 years; 82% were female, and median disease duration was 3 years. Just over half the cohort had interstitial lung disease, and 16% had pulmonary artery hypertension.

Among the anti-ENA autoantibody subtypes, anti-ACA was seen in 37% of patients, anti-Scl-70 in 24%, anti-RNP in 9%, and anti-RNAPIII in 5%; other subtypes were rarer. SSc-specific NVC patterns were seen in 88% of patients, with 10% of the cohort showing an early (less severe microangiopathy) pattern, 42% an active pattern, and 36% a late pattern.

One of the study’s objectives was to determine whether one or more mechanisms was responsible for both autoantibody production and the microangiopathy seen in SSc. If a joint mechanism is implicated, “more severe NVC patterns would be determined in patients with autoantibodies (such as anti-Scl-70 and anti-RNAPIII) that are associated with more severe disease,” wrote Dr. Markusse and her colleagues. “On the other hand, if specific autoantibodies and stage of microangiopathy reflect different processes in the disease, a combination of autoantibody status and NVC could be helpful for identifying patients at highest risk for cardiopulmonary involvement.”

The investigators reported finding a similar distribution of NVC abnormalities across the major SSc autoantibody subtypes (except for anti-RNP-positive patients), suggesting that combinations of the two variables would be most predictive of cardiopulmonary involvement. More severe NVC patterns were associated with a higher risk of cardiopulmonary involvement, independent of the presence of a specific autoantibody. Notably, the researchers wrote, “prevalence of ILD [interstitial lung disease] is generally lower among ACA-positive patients. According to our data, even among ACA-positive patients there was a trend for more ILD being associated with more severe NVC patterns (OR = 1.33).”

A similar pattern was seen for pulmonary artery hypertension. “Based on anti-RNP and anti-RNAPIII positivity, patients did not have an increased risk of a [systolic pulmonary artery pressure] greater than 35 mm Hg; however, with a severe NVC pattern, this risk was significantly increased (OR = 2.33).”

The investigators cautioned that their findings should be confirmed in larger cohorts. The study by Dr. Markusse and her colleagues was conducted outside funding, though manufacturers donated diagnostic antibody tests. One of the 11 study coauthors disclosed receiving financial support from Actelion.

Macitentan boosts quality of life in PAH patients

BY RANDY DOTINGA
Frontline Medical News

Macitentan, a recent addition to the drugs that treat pulmonary arterial hypertension (PAH), improves and stabilizes quality of life for patients with the condition, according to an industry-funded study.

Macitentan (Opsumit) remains tremendously expensive, costing as much as $100,000 per year in the United States, and the study provides little in the way of direct comparison to other drugs in its class. Still, the drug’s effects on quality of life are dramatic, said study lead author Sanjay Mehta, MD, FRCP(C), FCCP, professor of medicine at the University of Western Ontario and director of the Southwest Ontario Pulmonary Hypertension Clinic at the London (Ont.) Science Center.

Researchers found that those who took the 10-mg dose, versus placebo, reported significant improvement in seven of eight quality-of-life domains, and in physical and mental components scores, as measured by the 36-item Short Form Health Survey (SF-36). In addition, the study linked 10-mg doses, versus placebo, to a lower risk of a decline of three points or more in the physical component score (hazard ratio, 0.60; 95% confidence interval, 0.47-0.76; P < .0001) and the mental component scores (HR, 0.76; 95% CI, 0.61-0.95; P = .0173) until end of treatment.

“The drug has shown stability in patients’ quality of life over 6 months and 12 months,” Dr. Mehta said in an interview. “I can’t cure anybody, and they’ll get worse at some point, but I can improve them. They physically feel better, they’re less short of breath with less body pain, and they feel better psychologically.”

Macitentan, an endothelin receptor antagonist, received Food and Drug Administration approval in 2013 following a study that year (N Engl J Med. 2013 Aug 29;369[9]:809-18) that linked 10-mg doses to a significantly lower risk of death and various complications, compared with placebo and the 3-mg dose. The new study (Chest. 2017 Jan;151[1]:106-18) is an analysis of data from the 2013 study.

The PAH patients were randomly assigned to one of three groups: macitentan 10 mg once daily (234), macitentan 3 mg (237), and placebo (239). The study examined responses from 710 patients (76.9% were female, 55.2% were white, mean age was 45.5) to the SF-36 at baseline, 6 months, 12 months, and end of treatment.

Dr. Mehta noted that macitentan has not been clinically compared to the other drugs. The study, however, notes that it is the first PAH treatment to show improvement in seven of eight domains in the quality-of-life survey.

The study was funded by Actelion Pharmaceuticals, maker of macitentan. Dr. Mehta has received consulting and speaking fees and institutional support for clinical trials from Actelion, among other drug companies. The other authors report various disclosures, including relationships with Actelion.
A federal district court judge has blocked health insurer Anthem from acquiring Cigna, ruling the megamerger would violate antitrust laws and stifle competition.

The decision came weeks after another U.S. district court judge barred a merger between health insurance giants Aetna and Humana.

The U.S. Department of Justice praised the latest ruling, calling the decision a victory for patients. “This merger would have stifled competition, harming consumers by increasing health insurance prices and slowing innovation aimed at lowering costs of health care,” Acting Assistant Attorney General Brent Snyder said in a statement.

Anthem intends to appeal the decision, as combining Anthem and Cigna would positively impact the health and well-being of millions of Americans – saving them more than $2 billion in medical costs annually,” Mr. Swedish said in a statement. “If not overturned, the consequences of the decision are far reaching and will hurt American consumers by limiting their access to high-quality affordable care, slowing the industry’s shift to value-based care and improved outcomes for patients, and restricting innovation, which is critical to meeting the evolving needs of health care consumers.”

In a statement, a Cigna official said the company intends to carefully review the opinion and evaluate its options in accordance with the merger agreement.

“Cigna remains focused on helping to improve health care by delivering value to our customers and clients and expanding our business around the world,” the statement said.

The DOJ, 11 states, and the District of Columbia sued Anthem and Cigna in July over their proposed $54 billion consolidation in what would have been the largest merger in history.

The DOJ argued the merger would substantially harm competition and negatively impact the entire insurance industry if allowed to proceed. The consolidation would enhance Anthem’s power to profit at the expense of consumers and the doctors and hospitals who provide their medical care, DOJ attorneys said in their complaint.

Anthem and Cigna argued the proposed acquisition was “procompetitive,” and that the merger would result in efficiencies that would directly benefit consumers via greater access to affordable health care. The benefits of the merger outweigh any alleged anticompetitive effects, according to Anthem.

A trial before Judge Amy Berman Jackson of the U.S. District Court for the District of Columbia ran from November through January. Judge Berman’s opinion is temporally under seal to allow parties to review for confidentiality.

The ruling is the second victory for the DOJ in as many weeks. In a Jan. 23 decision, Judge John D. Bates of the U.S. District Court for the District of Columbia denied Aetna’s $37 billion plan to purchase Humana, following a month-long trial that began in early December. Judge Bates ruled the consolidation would violate antitrust laws and reduce competition. Aetna and Humana did not respond to requests for comment.

aga@frontlinemedcom.com
On Twitter @legal_med

Michael E. Nelson, MD, FCCP, comments: Any business owner who has been required to absorb yearly double-digit increases in employee health insurance costs cannot help but wonder where Mr. Swedish learned his “new math.” His second statement is even more incogitable – since when were insurers known for expanding access to health care. Anyone who has been unfortunate enough to participate in a peer-to-peer conference with an insurer in an attempt to get a patient needed care knows otherwise. Although health insurance companies did not exist in 1890, the Sherman Antitrust Act of the same year was perfectly scripted to proscribe this type of merger over a century later.
Trump travel policy may affect medical meetings

BY ALICIA GALLEGOS
Frontline Medical News

President Trump’s revised executive order blocking travelers from six Muslim-majority countries from entering the United States could land a damaging blow to global cooperation in scientific research and could impede assemblies of the world’s top medical experts.

The March 6 executive order bars citizens of Iran, Libya, Somalia, Sudan, Syria, and Yemen from obtaining visas for 90 days and blocks refugees from those countries from entering the United States for 120 days. The measure, which takes effect March 16, supersedes President Trump’s Jan. 27 travel ban. The new order exempts citizens of the six countries who are legal permanent U.S. residents or who have current visas.

The policy could have detrimental effects on future collaboration between U.S. and international scientists and may ultimately endanger the health and well-being of patients, said International Antiviral Society–U.S.A. executive director and president Donna M. Jacobsen.

There is “serious reason for concern” that the policy will dissuade scientists and researchers “from traveling to the United States in the future overall and sharing their work with colleagues here,” she said.

Thousands of academics from around the world, including physicians, researchers, and professors, have vowed to boycott U.S.-based conferences in light of the Trump administration policy.

The new executive order comes nearly 2 months after President Trump’s original travel ban caused nationwide protests and led to a series of legal challenges. The states of Washington and Minnesota, which sued President Trump over his original ban, argued that such a ban harms the teaching and research missions of their universities and prevents students and faculty from traveling for research and academic collaboration. In addition, the executive order restricts universities from hiring attractive candidates from countries affected by the ban, state officials said. A federal court temporarily blocked the original travel ban on Feb. 3, a decision upheld by the 9th U.S. Circuit Court of Appeals on Feb. 9. The circuit judges said the plaintiffs were likely to succeed in their arguments and that the president had demonstrated no evidence that his executive order advances national security.

The new executive order excludes Iraq and also removes language that had indefinitely banned Syrian refugees. In a March 6 memorandum, the White House said the purpose of the ban is to prevent “foreign nationals who may aid, support, or commit violent, criminal, or terrorist acts,” while the administration enhances the screening and vetting protocols and procedures for granting visas and admission to the United States.

“This nation cannot delay the immediate implementation of additional heightened screening and vetting protocols and procedures for issuing visas to ensure that we strengthen the security and safety of our country,” the memo states.

Societies voice concern for travel ban

February 7, 2017
The Honorable John F. Kelly
Secretary
U.S. Department of Homeland Security
Washington, DC 20528

Dear Secretary Kelly:
The undersigned organizations are greatly concerned that the executive order signed by President Trump on January 27, 2017 will result in discrimination against foreign-born persons from certain predominantly Muslim countries. We are particularly concerned that by restricting entry of physicians and medical students from seven designated Muslim-majority countries, the order will undermine medical education and result in patients losing access to their doctors. We are also greatly concerned that the 120 day ban on accepting refugees, and the indefinite ban on Syrian refugees, will contribute to an ongoing public health crisis for those affected, needlessly subjecting them to violence, injury, illness, deprivation and even death. While we are pleased that the courts have temporarily halted implementation of the executive order, the underlying issues of concern about the harm caused by the executive order remain.

The restrictions in the executive order will hinder the free exchange of information and travel among medical students, residents and physicians around the world and result in Americans having poorer access to care. In 2016, 3,769 non-U.S. citizen international medical graduates (IMGs) obtained first-year residency positions. More than half of internal medicine residency positions were filled by IMGs. Approximately 25% of the nation’s physicians are IMGs and provide a disproportionate share of the care to Americans in underserved communities that have a shortage of U.S. born and trained physicians. They also add necessary diversity and cultural competency to our healthcare workforce. If the executive order prevents IMGs from being able to come to the U.S. this could potentially affect the care for thousands of patients.

Our organizations are also especially concerned about refugees with dire medical conditions who had been approved for visas to enter the U.S. but since the executive order, have been unable to enter the country to receive much needed medical care.

While we urge that the executive order be rescinded and replaced with non-discriminatory policies that support families, public health, and medical education, and are pleased that the courts have temporarily halted implementation of the executive order, there are steps that DHS can take immediately to selectively ease travel restrictions that impact medical education, access to health care services, and public health for individuals who otherwise meet the criteria for immigration, including those from the seven countries identified in the executive order. Specifically, we urge the Department of Homeland Security to:

1. Reinstatement of the Visa Interview Waiver Program. Suspension of the program “risks creating substantial backlogs in the processing of new and renewal visas for trainees from any foreign country — delays that create substantial problems for residency programs with trainees on visas and that could interfere with the residency match process this year.”

2. Remove restrictions on entering the U.S. for physicians from the seven designated countries who have been approved for J-1 or H-1B visas and students from those countries with F-1 visas who have been accepted to U.S. medical schools.

3. Develop and implement a plan to allow physicians from the seven designated countries to obtain travel visas to the U.S. for medical conferences and other medical and research-related engagements.

4. Make it a priority to implement a process to admit refugees, without further delay, who had already been vetted and approved for entry prior to the executive order and who are in need of urgent medical care. We note that even with such revisions, the executive order will still inappropriately bar immigrants and refugees based on discriminatory criteria (religion and country of origin) including family members of physicians and medical students in the U.S.

Our organizations are committed to non-discrimination against physicians, medical students and others in immigration policies and offer our assistance in developing policies that support access to health care services, public health, and medical education while balancing the nation’s security needs. Until or unless the executive order is completely rescinded or permanently blocked, it is essential that DHS move forward to ensure that restrictions on physicians and medical students are not reimposed, and that priority is given to refugees with medical conditions needing treatment.

Sincerely,
Alliance for Academic Internal Medicine
American College of Chest Physicians
American College of Physicians
American Society for Gastrointestinal Endoscopy
American Society of Hematology
American Thoracic Society
Infectious Diseases Society of America
Renal Physicians Association
Society for Adolescent Health and Medicine
Society of Critical Care Medicine
Society of General Internal Medicine
The Mount Sinai Hospital - National Jewish Health Respiratory Institute brings together a strong, integrated program for diagnosis and treatment of respiratory illness and lung disease. Our pulmonologists collaborate with specialists in related disciplines and work closely with research scientists on precision medicine, genomics, and data-driven clinical protocols to enhance the quality and outcomes of the respiratory disease practice. Additionally, our experts are on the faculty of the Icahn School of Medicine at Mount Sinai, ranked among the nation's top medical schools by U.S. News & World Report.

- Asthma
- Bronchiectasis and NTM
- COPD
- Pulmonary Fibrosis/ILD
- Lung Nodule/Lung Cancer
- Pulmonary Hypertension
- Sarcoidosis
- Sleep Disorders
HFNC bests conventional O₂ therapy

By Whitney McKnight

From CHEST

In patients with acute respiratory failure, high-flow nasal cannula (HFNC) is more reliable than conventional oxygen therapy at reducing rates of endotracheal intubation, although no significant difference was found when HFNC was compared with noninvasive positive pressure ventilation, a new study found.

An increasing awareness of the high rate of adverse events and mortality rates associated with invasive mechanical ventilation in hospitals has led to a rise in the use of noninvasive positive pressure ventilation (NIPPV). While this has effectively cut the use of conventional oxygen therapy (COT), its application in clinical practice is limited by a host of complications such as interface intolerance, skin damage, and other hazards. HFNC, because of its demonstrated efficacy and relatively easier application, and better tolerance in patients, also has gaining popularity. Despite the known benefits of HFNC, this therapy is not given to all adults with acute respiratory failure (ARF). This may be due to the lack of consistency in data regarding how HFNC’s effectiveness at decreasing intubation and reintubation rates compares with COT’s and NIPPV’s.

Researchers in China conducted a meta-analysis and systematic review of all superiority and nonsuperiority data on the outcomes of using HFNC, COT, and NIPPV to treat respiratory failure (ARF). This may be of interest to the authors of the included trials, population, and study quality, there unsurprisingly is a significant I-squared statistic for high heterogeneity in outcomes between studies. As such, little conclusion can be drawn regarding whether HFNC would be more beneficial than NIPPV in a given patient. It is likely that HFNC is better in some patients, while NIPPV is more appropriate for others and this meta-analysis just doesn’t offer much in that regard.

Eric J. Gartman, MD, FCCP, is assistant professor of medicine at Brown University, Providence, R.I. He is an editorial board member of CHEST Physician.

Is HFNC better than NIPPV? It depends

The introduction of high-flow nasal cannula (HFNC) fundamentally has changed how patients with acute respiratory failure are treated — both in avoidance of intubation and prevention of reintubation. Its use is supported by some very high quality studies over the last few years done in a variety of types of critically ill patients. While its clinical superiority to noninvasive ventilation (NIV) is still open to debate, the comfort and other attributes that HFNC provides increasingly are making it the first-choice modality (e.g., the patient can continue to eat, talk, and wear for longer periods of time).

Regarding this meta-analysis, given that most would agree that both HFNC and NIV are better than COT, the outcomes of interest are possible cause of the statistical heterogeneity, the authors concluded. “The finding that rates of intubation in patients with acute respiratory failure are reduced with [HFNC] use when compared to standard oxygen administration has important implications for critical care practitioners,” said Danielle R. Ouellette, MD, FCCP, of Henry Ford Hospital, Detroit, in an interview. “It seems likely that this effect is a result of improvement in not only oxygenation, but also ventilation by such catheters. HFNC may be a useful adjunct not only in patients with respiratory failure, but also post-extubation, and may be more tolerable than noninvasive ventilation.”

China-Japan Friendship Hospital is continuing the search for more data on the success rates of HFNC and NIPPV at reducing intubation and mortality rates. The hospital is sponsoring a multicenter, randomized, noninferiority trial titled, “High Flow Nasal Cannula vs. NPPV in Moderate Chronic Obstructive Pulmonary Disease Exacerbation,” according to ClinicalTrials.gov. No results were available for this trial as of March 1.

wmcknight@frontlinemedcom.com
On Twitter @whitneymcknight

In ICU, pair MRSA testing method with isolation protocol

By Dan Watson

An ICU’s method of testing for methicillin-resistant Staphylococcus aureus (MRSA) should be paired with its patient isolation policy, according to researchers at the University of Colorado at Denver. In an ICU with all patients preemptively isolated, it is worth the added expense to opt for the polymerase chain reaction (PCR) test — which generates results in a few hours — so that patients negative for the infection can be moved out of isolation more quickly, wrote Melanie D. Whitington, PhD, and her coauthors. But if the ICU is isolating only MRSA-positive patients, the authors instead recommend the less expensive but slower chromogenic agar 24-hour testing.

The other two MRSA tests the researchers assessed — conventional culture and chromogenic agar 48-hour testing — are less expensive. But when paired with either ICU isolation policy, those tests lead to excessive inappropriate isolation costs while waiting for the results, the study investigators cautioned (Am J Infect Control. 2017 Jan 23. doi: 10.1016/j.ajic.2016.12.014). Adding together the cost per patient of the test, the “appropriate isolation costs,” and “inappropriate isolation costs,” the universal isolation policy is least expensive per patient with PCR, at $82.51 per patient. With conventional culture, which can take several days, this cost ballooned to $290.11 per patient, with high inappropriate isolation costs.

Doing the same math with the more targeted isolation policy, the least expensive screening method was the 24-hour chromogenic agar, at $8.54 per patient, while the expense of the PCR test made it the most expensive method when paired with this isolation policy, at $30.95 per patient.

“With knowledge of the screening test that minimizes inappropriate and total costs, hospitals can maximize the efficiency of their resource use and improve the health of their patients,” Dr. Whitington and her coauthors wrote.

dwatson@frontlinemedcom.com

Frontline Medical News
High NIV volume not a predictor of good outcomes

BY MARY ANN MOON
Frontline Medical News

Hospitals that frequently treat acute chronic obstructive pulmonary disease (COPD) exacerbations using noninvasive ventilation – a practice known to reduce mortality, length of stay, and the need for more invasive treatment – did not have better patient outcomes than did hospitals that used noninvasive ventilation less frequently, according to a report published in Annals of the American Thoracic Society.

Acute COPD exacerbations are “one of the few conditions with high-level evidence demonstrating the benefits of noninvasive ventilation in patients with respiratory distress,” and the treatment has been widely adopted for this patient population. However, for noninvasive ventilation to succeed, patients must be carefully selected and closely monitored, and a multidisciplinary team of nurses, respiratory therapists, and physicians must coordinate the treatment, often across multiple hospital settings, said Anuj B. Mehta, MD, of The Pulmonary Center, Boston University, and his associates.

Until now, it was not known whether hospitals with a high volume of noninvasive ventilation develop specialized expertise and thus deliver superior patient outcomes, or whether a high volume results from suboptimal patient selection or otherwise puts a strain on a hospital’s staff and thus produces poor outcomes. To examine this question, Dr. Mehta and his associates analyzed information in a database enrolling adults treated at 252 California hospitals for acute COPD exacerbation. They focused on 37,316 hospitalizations that occurred during a single year. Overall, 9.3% of these patients received noninvasive ventilation. The

“Contrary to our hypothesis, we did not observe significantly lower COPD mortality” in hospitals with high volumes of noninvasive ventilation, the researchers noted.

American Thoracic Society.

Acute COPD exacerbations are “one of the few conditions with high-level evidence demonstrating the benefits of noninvasive ventilation in patients with respiratory distress,” and the treatment has been widely adopted for this patient population. However, for noninvasive ventilation to succeed, patients must be carefully selected and closely monitored, and a multidisciplinary team of nurses, respiratory therapists, and physicians must coordinate the treatment, often across multiple hospital settings, said Anuj B. Mehta, MD, of The Pulmonary Center, Boston University, and his associates.

Until now, it was not known

Eric Gartman, MD, FCCP, comments: It is unclear what conclusions can be drawn from this study given the likely heterogeneity between the included hospitals. For instance, hospitals with high volumes of NIV use also seemed to have patients with more significant comorbidities – and thus it would not be appropriate to compare these high-acuity hospitals to lower acuity hospitals. Further, as mentioned in the article there are many other support systems and monitoring that potentially can affect the outcomes of these patients – and such factors would be very difficult to control for in an analysis like this.

OVER 10,000 IPF PATIENTS HAVE BEEN TREATED WITH OFEV WORLDWIDE

SLOW THE PATH OF IPF PROGRESSION

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

DISCOVER MORE ABOUT OFEV INSIDE.

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hepatic Impairment

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

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

FVC, forced vital capacity.
OFEV has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials3*

**INPULSIS®-1 (Study 2)**
- Adjusted annual rate of decline in FVC, mL/year: **-115**
- Relative reduction in FVC decline: **52%**
- Placebo (n=204)
- OFEV (n=309)
- P<.001 (95% CI=78, 173)

**INPULSIS®-2 (Study 3)**
- Adjusted annual rate of decline in FVC, mL/year: **-207**
- Relative reduction in FVC decline: **45%**
- Placebo (n=219)
- OFEV (n=329)
- P<.001 (95% CI=45, 143)

**TOMORROW (Study 1)**
- Adjusted annual rate of decline in FVC, mL/year: **-191**
- Relative reduction in FVC decline: **68%**
- Placebo (n=83)
- OFEV (n=84)
- P=.01 (95% CI=27, 235)

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

**IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT’D)**

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

**Gastrointestinal Disorders**

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

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

**Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.
3 out of every 10 patients on OFEV showed an improvement (≤0% decline) in lung function in the INPULSIS® trials

**INPULSIS®-1**

<table>
<thead>
<tr>
<th>%</th>
<th>OFEV (n=309)</th>
<th>Placebo (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>relative increase</td>
<td>18%</td>
</tr>
<tr>
<td>12%</td>
<td>absolute difference</td>
<td></td>
</tr>
</tbody>
</table>

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

**INPULSIS®-2**

<table>
<thead>
<tr>
<th>%</th>
<th>OFEV (n=309)</th>
<th>Placebo (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>relative decrease</td>
<td>43%</td>
</tr>
<tr>
<td>14%</td>
<td>absolute difference</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
A vitamin D supplement to patients can significantly mitigate their risk of developing acute respiratory tract infections, according to a recent study published by the BMJ.

“Existing epidemiological and in vitro data have prompted numerous randomized controlled trials to determine whether vitamin D supplementation can decrease the risk of acute respiratory tract infection,” wrote the authors of the study, led by Adrian P. Martineau, PhD, of Queen Mary University of London. “A total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date [but] all but one of these aggregate data meta-analyses reported statistically significant heterogeneity of...
OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests and a pregnancy test prior to initiating treatment with OFEV [see Warnings and Precautions]. Recommended Dosage: The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of the bitter taste. The effect of churning 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 patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg in patients with mild hepatic impairment (Child-Pugh A), the recommended dosage of OFEV is 150 mg twice daily approximately 12 hours apart taken with food. Dose 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 continued treatment. Dose modification or treatment interruption may be necessary 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, discontinuation of OFEV, or a dose reduction to 50 mg twice daily, which subsequently may be increased to the full dosage. In most patients, the event was of ≤ 3 months status prior to treatment with OFEV [see Use in Specific Populations]. Arterial Thromboembolic Events: Arterial thromboembolic events have been reported in patients taking OFEV in clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher vascular 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 arterial thromboembolic events in patients with mild hepatic impairment (Child-Pugh A), consider treatment interruption, or discontinuation of management for adverse reactions. CONTRAINDICATIONS: None WARNINGS AND PRECAUTIONS: Hepatic Impairment: Treatment with OFEV is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see Use in Specific Populations]. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV [see Dosage and Administration]. Elevated Liver Enzymes: In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (84%) of patients with ALT and/or AST elevations had < 2 times ULN [see Use in Specific Populations]. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modification or treatment interruption may be necessary for liver enzyme elevations. Gastrointestinal Disorders: Diarrhea: Diarrhea was the most frequent gastrointestinal adverse reaction reported in ≥ 10%, 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 treatment in 5% of patients compared to ≤ 1% of placebo-treated patients. Dosage modifi-
cations or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be continued 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, discontinuation of treatment with OFEV may be considered in 12% versus 3% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, the event was of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. In most patients, the event was of mild to moderate intensity. 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 persists despite appropriate supportive care including anti-emetic therapy, OFEV 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 persists despite appropriate supportive care including anti-emetic therapy, OFEV treatment interruption may be required. In most patients, the event was of mild to moderate intensity. TOXICITY: Based on findings from animal studies and its mechanism of action, OFEV may cause fetal harm when administered to a pregnant woman. Nintedanib caused emphysema-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis (at less than 1× and approximately 5 times the maximum recommended human dose [MRHD] in adults). Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV until pregnancy status is verified. [see Warnings and Precautions]; Liver Enzyme and Bilirubin Elevations 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: Diarrhea; Nausea [see Warnings and Precautions]; Hypertension; Abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness; Vomiting; Ischemia; Nervous systemic disorders: Dizziness; and Tinnitus; Weight loss; and Nutrition disorders: Decreasing appetite; and Hypersensitivity disorders: Rash; and Other symptoms: Postural hypotension; and Vascular disorders: Decreasing blood pressure; and Other symptoms: Anemia; and Other symptoms: Erythema multiforme. In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1% vs. 0.6%).}

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OFEV n=722</th>
<th>Placebo n=508</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Hepaticobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Hepaticobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreasing appetite</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>

In the phase 2 (Study 1 and phase 3 Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.3%), lung neoplasm malignant (0.7% vs. 0.2%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MAECI), 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 10% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction leading 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 events that led to discontinuation in OFEV-treated patients were diarrhea (4%), 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.

Continued on page 49
In suspected VAP, ultrashort antibiotics may work

BY AMY KARON
Fornum Medical News

Ultrashort courses of antibiotics led to similar outcomes as longer durations of therapy 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 VKUR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: See Data) Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage for the indicated population is 15% to 20%. Data:

OVERDOSAGE: Nintedanib is not expected to be significantly absorbed after oral administration. In humans, nintedanib is extensively metabolized by CYP3A4 and CYP2C8 in the liver. Nintedanib is metabolized by several pathways including oxidative, hydroxylative, glucuronidation, sulfation, and trans-sulfuration pathways. Nintedanib is highly bound to plasma proteins (99%). The primary metabolite, nintedanib glucuronide, is at least 10-fold lower than the parent compound in plasma. Nintedanib is excreted in the feces and urine (42% and 15%, respectively).

Nintedanib is metabolized to several active metabolites, including nintedanib glucuronide, nintedanib sulfate, and nintedanib sulfoxide. The metabolism of nintedanib is not affected by concomitant use of standard benzodiazepines or selective serotonin reuptake inhibitors. The metabolism of nintedanib is not affected by concomitant use of standard benzodiazepines or selective serotonin reuptake inhibitors. The metabolism of nintedanib is not affected by concomitant use of standard benzodiazepines or selective serotonin reuptake inhibitors.
Smoking cessation drugs’ warning labels are changing

BY WHITNEY MCKNIGHT
Frontline Medical News

Labels on two smoking cessation treatments will offer less severe warnings for mental health risk potentials in people with no history of psychiatric disorders, the Food and Drug Administration has announced.

Varenicline (Chantix) will no longer include a boxed warning for serious mental health side effects. The label for bupropion (Zyban) will still include a boxed warning, but language describing the potential for serious psychiatric adverse events will no longer appear within it. Updates will also be made to both labels to describe side effects on mood, behavior, or thinking.

“The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past,” FDA officials stated in an online notice.

In addition, varenicline’s label will reflect trial data showing its superior efficacy, compared with oral bupropion or nicotine patch. Although a patient medication guide will still be included with each prescription, the risk evaluation and mitigation strategy that prompted the guide will no longer be in place.

Earlier this year, two FDA advisory committees voted in favor of updating varenicline’s label, based on data from a randomized, controlled trial of more than 8,000 smokers, half of whom had a history of psychiatric disorders.

The trial showed no clinically significant difference in risk of adverse events across the smoking cessation treatments varenicline, bupropion, nicotine patch, or placebo study arms, although the risk was higher in the psychiatric cohorts in each. Overall, 2% of those without a history of mental illness experienced neuropsychiatric adverse events, compared with between 5% and 7% of those with such a history. Pfizer, maker of Chantix, and GlaxoSmithKline, maker of Zyban, cosponsored the trial.

FDA officials advised clinicians to guard against changes in mental health status in smokers using varenicline and bupropion, but noted that the results of the trial confirm the benefits of stopping smoking outweigh the risks of these medicines.

Continued from page 47

Results also demonstrated that bolus doses of vitamin D did not offer any beneficial value to subjects. Those who received daily or weekly doses without bolus had a better OR, compared with those who did receive at least one bolus dose: 0.81 (95% CI, 0.72-0.91) versus 0.97 (95% CI, 0.86-1.10), respectively (P = .05). Individuals whose baseline 25-hydroxyvitamin D levels were lower than 25 nanomols per liter experienced a greater benefit than those whose levels were above 25: OR of 0.30 (95% CI, 0.17-0.53) and OR of 0.75 (95% CI, 0.60-0.95), respectively (P = .006).

“Our study reports a major new indication for vitamin D supplementation: the prevention of acute respiratory tract infection,” Dr. Martineau and his coauthors concluded, adding that a potential application for these findings would be “the introduction of public health measures such as food fortification to improve vitamin D status, particularly in settings where profound vitamin D deficiency is common.”

The study was funded by a grant from the National Institute of Health Research.

Results are ‘underwhelming’

While the work undertaken by Dr. Martineau et al. is commendable, the results themselves are ultimately underwhelming. The study’s results are too heterogeneous and offer too slight a reduction in overall risk to justify a complete overhaul of clinical procedure and prescribing protocols.

These findings should not change clinical practice in any significant way, and there are other groups of individuals, such as those with low serum concentrations of vitamin D, that were omitted from this analysis altogether.

Mark J. Bolland, PhD, is an associate professor of medicine at the University of Auckland (New Zealand). Alison Avell, MD, is a professor at the University of Aberdeen.

Most smokers attempt quitting without meds

BY RICHARD FRANKI
Frontline Medical News

More than half of cigarette smokers have received advice to quit from a health care professional, but less than a third used medication or counseling in their cessation attempt, according to investigators from the Centers for Disease Control and Prevention.

In 2015, just over 57% of adult smokers said that a health care professional had advised them to quit in the past year. Of those who tried to quit, 29% used medication such as nicotine patches or gum, varenicline, or bupropion; 7% used counseling (including a stop-smoking clinic, class, or support group and a telephone help line); and 31% used counseling and/or medication, the investigators reported (MMWR. 2017;66[52]:1457-64).

Data from the 2015 National Health Interview Survey show that cigarette smokers who were white (60%) or of multiple races (70%) were the most likely to have a health professional tell them to quit, while Asians (34%) and American Indians/Alaska Natives (38%) were the least likely. Whites were most likely to use counseling and/or medication (34%) and Hispanics were least likely (19%), although the rate for American Indians/Alaska Natives was not reported because of a small sample size or large margin of error.

“It is critical for health care providers to consistently identify smokers, advise them to quit, and offer evidence-based cessation treatments, and for insurers to cover and promote the use of these treatments and remove barriers to accessing them,” the researchers noted.

VIEW ON THE NEWS

Study Smart

Customize your board review study plan with our in-person and on-your-own study tools. Review the most up-to-date content and earn CME credit and MOC points in pulmonary, critical care, sleep, and pediatric pulmonary medicine.

Live course registration now open.

Join us in Orlando, August 18-27.

Or, at your convenience:

Board Review On Demand

Prop for your board exam and review the latest recorded content from previously recorded chest pulmonary, critical care, sleep, and pediatric pulmonary board review courses. Available in video, audio, or as a bundle of both.

MOC Assessment and Improvement Modules

Evaluate your current practice and identify areas for improvement through 7 different modules.

CHEST SEEK™ Library Subscription

Stay on top of your practice, challenge your knowledge, and prepare for your board exam with the largest collection of seek questions ever offered. Access your subscription via mobile app or web browser.

New! CHEST SEEK® Library Subscription

Stay on top of your practice, challenge your knowledge, and prepare for your board exam with the largest collection of seek questions ever offered. Access your subscription via mobile app or web browser.

> Learn More boardreview.chestnet.org
Dear Colleagues,

It doesn’t seem possible, but I have just completed the first quarter of my term as your 79th President and recently returned from chairing my first board meeting – a scary experience to be sure. All in all, it went well. We officially offered Steve Welch the position of Executive Vice President, thereby ushering in one of our own to lead the organization. Steve has successfully served as CHEST’s interim EVP/CEO since May 2016, after 22 years of service with this organization, most recently as Senior Vice President of Publications and Digital Content. I am utterly and completely confident in our choice and want you to know he has the full backing of the board, the Past Presidents, and nearly every doctor he has come in contact with.

We also started the strategic planning process for the next 5 years. I am a big believer in planning and have confidence that the team of physicians and staff we have assembled to provide us with guidance will lead us through this process, and we will be a much stronger organization for it. I hope you will all take the opportunity to weigh in as we progress. Ideas from all parts of the organization will be needed so that we don’t miss opportunities for improvement.

One of our strategic areas of focus for the past 5 years is how we serve our international members. CHEST is now truly a global organization. Our international membership continues to grow, and that impacts all areas of the College. In 2016, we provided education for more than 4,300 international members through our national meeting and courses provided all around the globe. In addition, the College has, in partnership with Chinese CHEST leadership and ministry of health officials, led the effort to begin the first pulmonary and critical care fellowship training programs in China. This was an amazing undertaking. The first four graduates were introduced and honored at CHEST 2016, and 20 more are scheduled to graduate next year. An additional 25 more fellowship training programs are to start this next year, and the Chinese National Health and Family Planning Commission recently approved the program as one of only three official fellowship training programs in China. I firmly believe we will look back on this endeavor as one of the greatest accomplishments in our organization’s long and storied history. Countless lives of patients with pulmonary diseases and critical illness are likely to be saved or extended in that country because of this work.

This brings me to CHEST’s position on the travel ban recently imposed and currently on hold in the United States. We, along with 11 other medical societies, sent a letter to the Secretary of Homeland Security underscoring our concern for such a ban, as it could most definitely adversely affect health-care delivery worldwide in ways not previously contemplated. For example, international medical graduates reportedly make up 25% of our physician workforce and provide a disproportionate amount of care to underserved communities. Should we not allow them to come and train here, we could be putting those patients at risk. The ban could result in patients who need specialized health care being denied entrance to the country. We worry that our global physician colleagues will be unable to travel to the United States for educational programs meant to provide them with the tools they need to care for their patients back home. I encourage you to read the full letter if you are interested.

On a brighter note, the program committee is busy planning CHEST 2017, which will be held in Toronto, Oct 28 to Nov 1. Our theme is Team-Based: Patient-Centered. Our advanced practice providers, critical care nurses, and respiratory therapists, among others, will participate in the planning and help shape different aspects of the program. We encourage our physician members to invite a friend, and come and enjoy the meeting. The traditional CHEST program with simulation and interactive, interdisciplinary symposia will be back by popular demand. There will be something in this meeting for everyone. I would be remiss if I didn’t mention that we are working closely with the American Board of Internal Medicine on Maintenance of Certification (MOC) and getting credit by using CHEST products, such as CHEST SEEK, e-learning modules, and live learning opportunities. In fact, CHEST 2016 made getting MOC points easy. Much of the program this year will qualify for MOC, and I would encourage you to take advantage of it. For those who I have had the pleasure of working with and hearing from this year, I thank you for your comments, welcome all opinions, and hope to hear from any member who has something CHEST-related on their mind.

Gerard A. Silvestri, MD, MS, FCCP
President

---

This month in CHEST

Editor’s picks

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

GIANTS IN CHEST MEDICINE

Paul M. O’Byrne, MBBCh, FCCP
By S.E. Wenzel, MD.

ORIGINAL RESEARCH

By F.E. Aleva, MD, et al.

COMMENTARY

The American College of Radiology Lung Imaging Reporting and Data System: Potential Drawbacks and Need for Revision.
By H.J. Mehta, MD, et al.

SPECIAL FEATURE

Improving the Management of COPD in Women.
By C.R. Jenkins, MD, et al.

---

Plan to attend CHEST 2017 in Toronto

Oct 28 – Nov 1
Toronto, Ontario, Canada

Join us in wonderful Toronto for CHEST 2017, where we’ll connect a global community in clinical chest medicine. Our program will deliver current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats. Take advantage of these opportunities to get involved now:

Submit Abstracts and Case Reports
Submission deadline: March 31
Submit an abstract of your original investigative work, case reports, and clinical case puzzlers for presentation at CHEST 2017. Submission is free, and accepted abstracts become eligible for investigative awards from the CHEST Foundation. Accepted abstracts and case reports (excluding clinical case puzzlers) will be published in an online supplement to the journal CHEST. Slide or poster presentations will be considered, along with poster discussion presentations for abstracts. Four types of case reports will be considered:
• Fellow Case Reports.
• Medical Student/Resident Case Reports.
• Global Case Reports.
• Clinical Case Puzzlers. Learn more and submit at chest2017.abstractcentral.com.

Apply for 2017 CHEST Foundation Grants
Application deadline: March 31
The CHEST Foundation has started accepting applications for its clinical research, distinguished scholar, and community service grants. Every year, the CHEST Foundation awards more than a half-million dollars to the next generation of lung health champions. The grants available are:
• GlaxoSmithKline Distinguished Scholar Research Grant in Respiratory Health: $150,000 over 3 years
• CHEST Foundation Research Grant in Lung Cancer: $50,000-$100,000* over 2 years
• CHEST Foundation Research Grant in Pulmonary Arterial Hypertension: $25,000 1-year grant
• CHEST Foundation and Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency: $25,000 1-year grant
• CHEST Foundation Research Grant in Nontuberculous Mycobacteria: $10,000-$30,000* 1-year grant
• CHEST Foundation Research Grant in Venous Thromboembolism: $30,000 1-year grant

Continued on page 53
The power of flexibility is yours with REVATIO Oral Suspension

With REVATIO you have 3 dosage forms to treat pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

Choose your dosage form based on each patient's needs.

To learn more, please visit REVATIOHCP.com

Indication
REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH): oral suspension, tablet, and injection.

Limitation of Use:
Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Important Safety Information
REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension.

REVATIO is contraindicated in patients with concomitant use of riociguat, a soluble guanylate cyclase (sGC) stimulator medication. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat.

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any other ingredient in REVATIO. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction has been reported in association with the use of sildenafil.

Use of REVATIO, particularly chronic use, is not recommended in children.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, iraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbitalurates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, is expected to cause substantial decreases in plasma levels of sildenafil. Treatment with doses higher than 20 mg three times a day is not recommended.

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

Patients with retinitis pigmentosa and patients on bosentan did not participate in the preapproval clinical trial. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

At doses higher than the recommended 20 mg TID, there was a greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

No dose adjustment required for renal impaired.

No dose adjustment required for mild to moderate hepatic impaired. Severe impairment has not been studied.

REVATIO is available in the following dosage forms:
- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

Please see brief summary of Full Prescribing Information on following pages.
INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise capacity and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominantly patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

DOSEAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension

The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Administer REVATIO doses 4-6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.

Reconstitution of the Powder for Oral Suspension

1. Tap the bottle to release the powder.
2. Remove the cap. 3. Accurately measure 60 mL of water and pour the water into the bottle.
4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 9. Press the bottle adapter into the neck of the bottle. The adapter is provided so that you can fill the oral syringe with medication from the bottle.
10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constituted).

INCOMPATIBILITIES

Do not mix with any other medication or additional flavoring agent.

CONTRAINDICATIONS

REVATIO is contraindicated in patients with concomitant use of organic nitrates in any form, either regularly or intermittently, because of the greater risk of hypotension [see Warnings and Precautions]. Concomitant use of nitrates, a guanylate cyclase stimulator, PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of riociguat. REVATIO is also contraindicated in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction, has been reported in association with the use of sildenafil.

WARNINGS AND PRECAUTIONS

Mortality with Pediatric Use

In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and 1 cause of death was typical of PAH. Use of REVATIO, particularly chronic, is not recommended in children [see Use in Specific Populations].

Hypotension

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be excessively affected by such vasodilatory effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

Worsening Pulmonary Vascular Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary vено-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with vено-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

Epistaxis

The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. The incidence was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is not known in patients with platelet dysfunction disorders.

Visual Loss

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged ≥50 years per the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with an increased risk of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO.

Hearing Loss

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have played a role. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying vascular risk factors for hearing loss, a combination of these factors, or to other factors. Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including REVATIO.

Combination with Other PDE-5 Inhibitors

Sildenafil is also marketed as VAGRA®. The safety and efficacy of combinations of REVATIO with VAGRA® or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VAGRA® or other PDE-5 inhibitors.

Priapism

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Vaso-occlusive Crisis in Patients with Pulmonary Hypertension Secondary to Sickle Cell Anemia

In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness and safety of REVATIO in the treatment of PAH secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

Clinical Trials Experience

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical trial and an open-label extension study in 277 REVATIO-treated patients with PAH WHO Group I.

The overall frequency of discontinuation in REVATIO-treated patients on 20 mg three times a day was 3% and was the same for the placebo group. In Study 1, the adverse reactions that were reported to occur more frequently in REVATIO-treated patients (20 mg three times a day) were more frequent in REVATIO-treated patients than in placebo-treated patients are shown in Table 1. Adverse reactions were generally transient and mild to moderate in nature.

Table 1: Most Common Adverse Reactions in Patients with PAH in Study 1 (More Frequent in REVATIO-Treated Patients than Placebo-Treated Patients and Incidence ≥3% in REVATIO-Treated Patients)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo, % (n=70)</th>
<th>REVATIO 20 mg three times a day, % (n=68)</th>
<th>Placebo-Subtracted, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>3</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Erhyma</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dyspea exacerbated</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Rinihtis</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Sinutis</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrea, myalgia and visual disturbances. Visual disturbances were identified as mild and transient, and were predominately color-tinge to vision, but also increased sensitivity to light or blurred vision.

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0% placebo and for all REVATIO doses studied was 1.9% versus 0% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). 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.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular and cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhage have been reported in hemodyalized patients. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after use of sildenafil without sexual activity. Others were reported to have occurred up to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system

Seizure, seizure recurrence.

DRUG INTERACTIONS

Nitrates

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A4 Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended.
Other drugs that reduce blood pressure
Alpha blockers. In drug-drug interaction studies, sildenafil (5 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic. Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis).

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery have not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

when REVATIO is administered to a nursing woman. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

No dose adjustment is required (including severe renal impairment).

Patients with Renal Impairment

No dose adjustment is required (including severe renal impairment CLcr < 30 ml/min).

PATIENT COUNSELING INFORMATION

Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only

Rev. June 2015

Continued from page 50

• CHEST Foundation Research Grant in Pulmonary Fibrosis: $30,000 1-year grant
• CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease: $50,000 1-year grant
• CHEST Foundation Research Grant in Women’s Lung Health: $10,000 1-year grant
• CHEST Foundation Research Grant in Asthma: $15,000 – $30,000* 1-year grant
• CHEST Foundation Research Grant in Cystic Fibrosis: $30,000 1-year grant
• Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP: multiple awards up to $15,000 per 1-year grant

*Amount contingent on funding.

Apply for grants at chestfoundation.org/grants.

Catching up with our CHEST Past Presidents

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

James A.L. Mathers Jr., MD, FCCP

President 2008-2009

It was a great honor to be inaugurated as President of the American College of Chest Physicians at the 2008 Annual Meeting in Philadelphia. My chosen vocation was community-based private practice, and from my early years in practice, I found the opportunity to interact with the clinically oriented scholars of CHEST invaluable. My wife Susan and I fondly remember activities with staff, others in leadership, and their families. My immediate goals for my presidential year were to ensure the financial security of the College, in light of the evolving restrictions on industry funding, and to raise the profile of telemedicine for the care of patients with chronic conditions and the critically ill. However, that year is probably most remembered for the unanticipated need to formulate a step-down agreement with then-CEO Alvin Lever, who had served the College and an unprecedent 17 years. To assist with financial planning, we were able to engage Master’s degree candidates from the Kellogg School of Business at Northwestern University in Evanston, Illinois, to perform a detailed cost and benefit analysis of our programs and to help develop recommendations for streamlining and improving our budgeting process. In partnership with the American Thoracic Society, the Society of Critical Care Medicine, and the American Association of Critical-Care Nurses, we developed a grant proposal to host a multisociety conference to examine the use of telemedicine for the care of critically ill patients. The grant was funded by the National Institutes of Health, and the results of the conference were published in CHEST. Following my presidential year, I continued to speak at numerous meetings about the potential for telemedicine to improve the care of patients with pulmonary disease. I retired from my community-based private practice at the end of 2010. Susan and I divide our time between Richmond, Virginia, engaging with our grandchildren, and the west coast of Florida, where I am working on my saltwater fishing credentials. Regular rounds of golf with former colleagues, some retired and some still in practice, keep me abreast of the pressures on and changes in the clinical environment.

Early in my practice, I became interested in addressing federal policies that interfered with the ability to provide state-of-the-art care to my patient population. My first committee appointment with CHEST was the Government Relations Committee. Our activities were closely coordinated with the National Association for Medical Direction of Respiratory Care (NAMDRC) and the American Thoracic Society. During my year as Immediate Past President of the College, I was approached by NAMDRC and invited to write their monthly publication, The Washington Watchline. I have continued to enjoy that opportunity, as well as interacting with their membership. When called upon by NAMDRC, I travel to Washington, DC, to meet with Medicare staff to discuss policy issues important in the care of pulmonary patients.
Household air pollution: Foundation grantee champions lung health

BY CATHERINE OBERG, MD

In 2016, Catherine Oberg, MD, was awarded the CHEST Foundation Research Grant in Women’s Lung Health for her project on household air pollution in Ghana. In this recent interview with Dr. Oberg, she describes how she is championing lung health.

How I got involved

In medical school, I was very interested in international medicine and took a trip to Tanzania to do primary care work when I was in my fourth year. I saw firsthand how the people, women especially, sleep, cook, eat, and take care of their children and animals all in one house. I saw how direct smoke exposure from cooking caused symptoms of cough, phlegm, and shortness of breath. I knew this was an area where I could make an impact.

When you’re looking for grants to do this kind of work, it’s a very nebulous area. Fortunately, I learned about CHEST Foundation grants through my mentor, Alison Lee, MD, who was a CHEST Foundation grant recipient early in her career. With the help of the grant, I was able to furnish my own supplies, get everything to Ghana, train native health-care providers, and start doing assessments. I received the CHEST Foundation grant at the perfect time. I am so appreciative and honored to be a CHEST Foundation grant recipient. It’s such a humbling experience to be able to act on these things that I’ve been looking into for so many months. I’m just excited and thankful, and can’t wait to see what we’re able to show.

Tackling a leading cause of lung disease

In rural areas around the world, people cook with ineffective fuels, such as animal dung, that cause damaging household air pollution. This is a leading cause of asthma, COPD, and lung cancer worldwide, and it preferentially affects women and children because of their roles in the household. My project focuses on household air pollution with a goal to measure the effectiveness of utilizing a clean burning stove as an intervention.

We have a cohort of women in Ghana and have had randomized clusters using either a liquefied petroleum gas (LPG) clean burning stove or a traditional cook stove for 18 months now. We’re going to look at their lung function, inflammatory markers, and respiratory symptoms and compare the groups to see if the intervention has made a difference.

The impact

Being able to breathe is a function many of us take for granted. The ability to impact something this vital to everyday life is a really exciting and important challenge. It’s an area where I think we can make a big impact.

This grant is allowing us to run our entire inflammatory marker component. As we are learning more about asthma and COPD, we’re seeing phenotypes of people that don’t fit the standard. This cohort of women illustrates that heterogeneity of disease, as we’re seeing more overlap in the symptoms they have. Currently, there are really no data looking at this, and we now have the resources to dive into this research.

The future

This project could bring about further research and hopefully provide evidence supporting these types of interventions. The impact could affect millions of people around the world. The CHEST Foundation grant is providing materials that are the foundation of our project. This grant allows us to design better studies in the future, to educate patients in a more effective manner, and to prevent these life-threatening diseases.

The next CHEST Foundation grants cycle is open from February 1 to March 31, 2017. How will you champion lung health? Learn more about foundation grants and how you can apply at https://chest.realмагнет.land/chest-foundation-grants.
Alternative to 10-year ABIM exam starts 2018

On December 14, the American Board of Internal Medicine (ABIM) announced an alternative to the 10-year Internal Medicine recertification exam, effective 2018. Currently, ABIM board-certified physicians can participate in Maintenance of Certification (MOC) by earning 100 MOC points every 5 years and passing a maintenance of certification exam every 10 years. Beginning in 2018, physicians who are certified by the ABIM in Internal Medicine will have the option to take a lower-stakes exam every 2 years, rather than taking the current high-stakes exam every 10 years. The low-stakes exam option provides greater flexibility to the diplomate by allowing one to complete the examination at a convenient time set by the physician at home or in the office. While this new option will initially be available only to Internal Medicine diplomates, the ABIM intends to extend this alternative recertification model to subspecialties in the future.

CHEST is exploring how our education will evolve to address these key changes. For additional information, please visit ABIM’s website.

Pulmonary Hypertension Care Center initiative moves forward

The Pulmonary Hypertension Association (PHA) launched its Pulmonary Hypertension Care Center (PHCC) initiative 2 years ago. This initiative was designed to raise the quality of care, as well as long-term outcomes for this disease that is often misdiagnosed and progressive. The PHCC program has designated 41 adult and 6 pediatric sites as Comprehensive Care Centers with ongoing accreditation of new sites. As part of this program, the PHA Registry was established to provide input to improve the care of PH patients. The PHA Registry (PHAR) is a multicenter, prospective observational registry of newly evaluated patients with pulmonary arterial hypertension (PAH) and has enrolled 200 patients to date. PHAR participation is open to any PHCC-accredited center.

PHCC accreditation has two pathways: Comprehensive Care Centers and Regional Care Centers. Accreditation is based on adherence to consensus guidelines for the diagnosis and treatment of PH, the scope of PH-related services provided at the center, and the expertise of the center’s PH Care Team members.” PHCC accreditation is potentially available to all PH centers that meet the established criteria that can be found at the PHCC website.

Additional information may be found at the PHCC website (https://phassociation.org/PHCareCenters).

Calls for faculty participation in the CHEST PREP program

About PREP
The CHEST PREP Clinical Immersion program is an unbranded, disease-state program that educates industry members and partners to advance their knowledge into understanding that builds their confidence for engagement in clinical conversations with health-care teams.

2. The CHEST PREP program is seeking interest-ed CHEST members in Chicago-based institutions to consider participating as faculty presenters in the following disease areas: COPD, Asthma, PAH, CTEPH, IPF, SCLC, and NSCLC.

Continued on following page
In late 2015, Congress passed the Bipartisan Budget Act (BBA) to address numerous wide-ranging budget concerns, including issues related to agriculture, pensions, the strategic petroleum reserve, along with some Medicare issues. Section 603 of BBA is now coming back to haunt pulmonary rehabilitation services.

The intent of Section 603 is reasonable – to address the phenomenon of hospitals purchasing physician practices to take advantage of payment differentials between identical or virtually identical services when comparing the hospital outpatient prospective payment system (HOPPS) and the physician fee schedule (PFS). For example, an orthopedic practice might own its own MRI and related support services. It will bill for those services under the PFS. However, if the practice sells that segment of the revenue stream (the MRI assets, etc) to a hospital, the hospital can bill Medicare for those same services under the hospital outpatient prospective payment system at an amount notably higher than the PFS payment.

To address this payment aberration, Congress instructed the Centers for Medicare & Medicaid Services to craft a system to preclude a hospital from such behavior. If a hospital wishes to expand its current program and bill under the hospital outpatient methodology MUST do so by expanding at its current location. An expansion at a new location that is not within 250 yards of the main hospital campus triggers Section 603 provisions.

A hospital that wishes to expand its current program and bill under the hospital outpatient methodology MUST do so by expanding at its current location. An expansion at a new location that is not within 250 yards of the main hospital campus triggers Section 603 provisions.

Medicare Payments for HCPCS code G0424 through the physician fee schedule

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Payments</th>
<th>Pulm Disease Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>$688,489.27</td>
<td>$340,805.64</td>
</tr>
<tr>
<td>2013</td>
<td>$589,116.95</td>
<td>$310,065.29</td>
</tr>
<tr>
<td>2014</td>
<td>$535,512.81</td>
<td>$229,832.58</td>
</tr>
</tbody>
</table>

(Source: Physician Supplier Procedure Summary File)
Continued from previous page

of the main hospital campus, the outpatient billing methodology is permitted. Likewise, if expansion of a current off-campus service occurs at the same location of the current off-site service, the hospital may continue to bill under the outpatient rules. Several other technical exceptions are permitted, for example construction planned prior to passage of BBA.

The implications for pulmonary rehabilitation are critical to its evidence that pulmonary practices simply do not provide pulmonary rehab services.

These data strongly indicate that G0424 pulmonary practice physician office billing for the most recent year data are available ($230K), compared with hospital outpatient allowed charges ($119M), is less than two-tenths of 1% of billing through the hospital setting. To argue that hospitals are purchasing pulmonary practices for financial gain tied to pulmonary rehab services defies

While congressional logic may be relatively understandable, for pulmonary medicine, it is based on the premise that a hospital would purchase a pulmonary practice because that practice had a lucrative pulmonary rehabilitation services cash flow. NAMDR and other societies were able to document major flaws in the basic premise, resulting in very problematic unintended consequences.

growth. A hospital that wishes to expand its current program and bill under the hospital outpatient methodology MUST do so by expanding at its current location. An expansion at a new location that is not within 250 yards of the main hospital campus triggers Section 603 provisions, and the hospital will bill at the physician fee schedule rate. Because the PFS payment rate is just over half of the payment rate for HOPPS payment, it is unlikely that a hospital would expand an existing program or establish a new one if it would be forced to bill under the lower rate.

While congressional logic may be relatively understandable, for pulmonary medicine, it is based on the premise that a hospital would purchase a pulmonary practice because that practice had a lucrative pulmonary rehabilitation services cash flow. NAMDR and other societies were able to document major flaws in the basic premise, resulting in very problematic unintended consequences. A detailed review of Medicare data, as well as financial logic. If the CMS premise was valid, one would expect the aggregate physician office billing to be much greater than $535K.

In discussions with CMS, the Agency did agree that there are likely to be unintended consequences related to Section 603 implementation. The Agency also emphasizes that it does not have the statutory authority for a “carve out” exemption. CMS stated that even if it agreed with us, it simply lacked the authority to exempt pulmonary rehab services. CMS also agreed that there is growing evidence that pulmonary rehab is a underutilized service that may very well save the program money through reduced hospitalizations and rehospitalizations, but it has little choice to implement the statute as Congress so mandated.

Therefore, the only solution is a legislative one. NAMDR and other societies are seriously considering approaching Congress for such resolution.

In memoriam

Sy lvan Lee Weinberg, MD, FCCP, MACC, a Past President of the American College of Chest Physicians (1983-1984), died Jan 17, 2017, in Dayton, Ohio. Dr. Weinberg was born in Nashville, TN, and received both his bachelor of science and doctor of medicine degrees from Northwestern University in Evanston, IL. He spent his time as an intern, medical resident, and fellow in cardiology at the Michael Reese Hospital in Chicago and went on to serve as a physician at Good Samaritan Hospital in Dayton, Ohio, for more than 40 years, ultimately becoming chief of cardiology and founder of the first coronary care unit in Ohio. Dr. Weinberg was also a clinical professor of medicine at the Wright State University School of Medicine in Dayton, and led a group cardiology practice until his retirement in 2000.

A past president also of the American College of Cardiology (ACC) and the Montgomery County Medical Society, Dr. Weinberg was the founding editor of the American Heart Hospital Journal, founding co-editor of Heart & Lung, and founding editor of the Journal of The Heart Institute of Dayton. He also was associate editor of the AMA Archives of Internal Medicine, the ACC Review Journal, and served on numerous editorial boards, including CHEST, the Journal of the American College of Cardiology, and the Clinical Cardiology and Heart Journal, formerly the British Heart Journal. He was editor-in-chief of ACC’s ACCEL audio journal for 15 years, recognized and known as, “the voice of cardiology,” traveling around the world and interviewing the world’s leaders in cardiology.

CHEST extends its heartfelt condolences to Dr. Weinberg’s family and friends.

Connect to CHEST members and leaders

Build your network and access the CHEST Member and Leader Directory. Use the directory to search for members and leaders. Easily search by name, specialty, location, or CHEST committee name to find others in the CHEST community. All members current in their dues are included in the directory.

Access to the directory is an exclusive CHEST member benefit. To view the directory, visit the following address: https://www.chestnet.org/Get-Involved/Membership/Member-Directory.

GO424 total allowed charges though hospital outpatient prospective payment

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Allowed Charges</th>
<th>Unique # of Providers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>$108,515,429</td>
<td>1,260</td>
</tr>
<tr>
<td>2013</td>
<td>$115,238,410</td>
<td>1,320</td>
</tr>
<tr>
<td>2014</td>
<td>$119,809,898</td>
<td>1,350</td>
</tr>
</tbody>
</table>

(Source: 100% Outpatient SAF)
Disaster Response

Mass shootings

There are multiple definitions for a mass shooting. Some definitions require a certain number of people to be killed. Some definitions require a certain number of people to be shot. Some definitions do not include gang violence. Regardless of the definition used, the number of mass shootings in the United States is increasing. There are also multiple definitions of what qualifies as a medical disaster. These definitions can be summarized with the statement that a medical disaster is an event that produces a number of casualties that overwhelms the local health system.

In the first 31 days of 2017, there have been 30 shootings in the United States, in which four or more people were injured (www.gunviolencearchive.org/reports/mass-shooting). On average, 309 people are shot every day in the United States. Ninety-three (30%) of those victims die of their injuries (www.bradycampaign.org/key-gun-violence-statistics). Most mass shootings fit the definition of a medical disaster. When a mass shooting occurs, medical resources are diverted from current patients to those injured in the shooting. Patients with acute medical problems unrelated to the shooting must endure a prolonged wait for medical care.

The CHEST Disaster Response NetWork feels that it is necessary to take action to reduce the number of mass shootings. Unlike natural disasters, mass shootings are man-made. As such, we should proactively work to prevent them. Prevention is a large part of medicine. Working together with community leaders, law enforcement, and government officials, we can and should work to eliminate mass shootings so that we can minimize gun-related injury and death.

John Gaillard, MD, FCCP
Steering Committee Member

Practice Operations
MACRA: Reincarnation of Medicare physician reimbursement model

In April 2015, President Obama signed the Medicare Access and CHIP Reauthorization Act (MACRA) eradicating the detested sustainable growth rate (SGR) formula. If this is your first dive into MACRA as an eligible professional (EP), it may be a bit baffling trying to understand its impact on your practice. MACRA affects physician offices, not hospitals. For 2017-2018, EPs include physicians, physician-assistants, nurse practitioners, clinical nurse specialists, and nurse anesthetists. Providers in their first year of Medicare participation or with a low Medicare volume are excluded. Additionally, there are two participation pathways, Merit-Based Incentive Payment System (MIPS), which combines the current Physician Quality Reporting System, Value Modifier, and Meaningful Use programs into a single pay-for-performance payment system; or Alternative Payment Models (APMs) that provide incentives in certain alternative payment models based on proposed CMS criteria. Accountable Care Organizations, Patient-Centered Medical Homes, Medicare/Medicaid Shared Savings Program, and Pioneer ACO program.

The FIRST Alcohol and other drug poisoning guideline has been released by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The guideline is the first of its kind to provide recommendations for both alcohol and other drug poisoning. The guideline is intended to help healthcare providers improve the care for patients who present with alcohol and other drug poisoning. The guideline includes recommendations for the evaluation, treatment, and discharge of patients with alcohol and other drug poisoning.

The guideline is available at https://www.niaaa.nih.gov/for-professionals/guidelines/alcohol-other-drug-poisoning.

Dr. Anum

CLASSIFIEDS

Also available at MedJobNetwork.com

PROFESSIONAL OPPORTUNITIES

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

Cambridge Health Alliance (CHA) is a well respected, nationally recognized and award-winning public healthcare system, which receives recognition for clinical and academic innovations. We have an excellent opportunity for a Pulmonary/Critical Care Physician to join our well established Pulmonary Division. Our system is comprised of three campuses and an integrated network of both primary and specialty care practices in Cambridge, Somerville and Boston’s Metro North Region. CHA is a teaching affiliate of both Harvard Medical School (HMS) and Tufts University School of Medicine.

Ideal candidate will be FT, BC in Pulmonary, Critical Care and Sleep as well as possess a strong interest in resident and medical student teaching. Excellent clinical/communication skills as well as a strong commitment to serve our multicultural underserved patient population is required. This position has both inpatient and ambulatory responsibilities. We offer a supportive and collegial environment with a strong infrastructure, inclusive of an electronic medical records system (EPIC). Candidates will have the opportunity to work in a team environment with dedicated colleagues similarly committed to providing high quality healthcare. Our employees receive competitive salary and excellent benefits. Please send CV’s to Deanna Simularis, Department of Physician & PA Recruitment, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge, MA 02138, via fax (617) 665-3553, or via e-mail: Simmons.harvard.challiance.org. We are an equal opportunity employer and all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability status, protected veteran status, or any other characteristic protected by law.

www.challiance.org

NORTH CAROLINA

BC Pulmonary/CC/Sleep Medicine physician opportunity, hospital-employed practice (Sleep Medicine optional). Base + wRVU annual quality bonus available, plus incentives/benefits. Comprehensive Cancer Center & clinical trials. EBUS/Navigational Bronchoscopy. No Visa Sponsorship. No firms. Send CV to:

Lilly Bonetti
Pardee UNC Health Care
Hendersonville, NC
Lillian.bonetti@unchealth.unc.edu
www.pardeehospital.org
(828) 694-7687

FIND YOUR NEXT JOB AT

MEDJOBNETWORK.COM

The first mobile job board for Physicians, NPs, and PAs

The first mobile job board for Physicians, NPs, and PAs. Access MedJobNetwork.com on your smartphone or tablet. Advanced Search Capabilities—search by specialty, job title, geographic location, employers, and more.

Drew Endy
Tel: (215) 657-2319
dendy@frontlinemedcom.com

Moving?

Look to Classified Notices for practices available in your area.

Disclaimer

CHEST PHYSICIAN assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.
and Bundled Payment Models are a few examples of an APM.

Under MIPS, rules are divided into four categories. During the first year, each category will make

**MACRA affects physician offices, not hospitals.** For 2017-2018, [eligible professionals] include physicians, physician-assistants, nurse practitioners, clinical nurse specialists, and nurse anesthetists.

up a certain percentage to the physician’s overall score, which will result in a penalty or payment as a lump sum in 2019. If you are an Advanced APM in 2017 and receive 25% of Medicare payments or see 20% of your Medicare patients through this model, you can earn up to a 5% incentive payment in 2019.

The performance period started on January 1, 2017. Submission of performance data is due by March 31, 2018. MACRA is complicated and here to stay. Learn and educate yourself to avoid down-

March 31, 2018. MACRA is complicated and here to stay. Learn and educate yourself to avoid down-

ment can be done at http://boardreview.chest-

.net.org.

Published guidelines on pharmacologic therapies for the treatment of asthma during pregnancy are available from the National Institute for Health and Care Excellence (NICE) (2007) and from the American College of Obstetricians and Gynecologists (ACOG) (2012). These guidelines recommend the use of ICS as the initial therapy for asthma during pregnancy. However, studies have shown that asthma control remains poor during pregnancy, leading to increased risk of hospital readmissions and acute rejection following lung transplantation. (Wilson et al. J Heart Lung Transplant. 2016;35[2]:173-178).

In a cohort of lung transplant recipients, frail patients had increased 1-year mortality (21.2% increase) and 3-year mortality (24.6% increase), compared with nonfrail patients (Wilson et al. J Heart Lung Transplant. 2016;35[2]:173-178). In a cohort of patients on the lung transplant waiting list, frailty was associated with an increased risk of delisting or death before lung transplantation (Singer et al. Am J Respir Crit Care Med. 2015;192[11]:1325-1334). In addition, frailty may be associated with an increased risk of hospital readmissions and acute rejection following lung transplantation (Wilson et al. J Heart Lung Transplant. 2016;35[4]:S197). Remaining challenges include determining which clinical assessments best define frailty in the lung transplantation population, documenting the adverse effects of frailty in well-designed multicenter prospective studies, and developing interventions to mitigate the adverse effects of frailty.

**Women’s Health**

**Asthma treatment during pregnancy**

Asthma is common in pregnancy, occurring in 3% to 8% of pregnant women. While the course of asthma during pregnancy is variable, the objectives of asthma treatment do not change and aim to prevent acute exacerbations and optimize management. Uncontrolled asthma is associated with an increased risk of perinatal morbidity. Published guidelines on pharmacologic therapies during pregnancy recommend the same step-wise approach as in nonpregnant women. Despite this, many providers are reluctant to prescribe medications during pregnancy, and data show a reduction of refills of asthma medications during pregnancy, likely due to safety concerns. Some recent studies have suggested an increase in major congenital anomalies among pregnant asthmatics using ICS (Garne E et al. BJOG. 2016;123[10]:1609-18), albeit with wide confidence intervals. These findings have not been con-

sistently confirmed (Kallen B et al. Eur J Clin Pharmacol. 2007;63:383-8). Furthermore, studies showing a dose response association of ICS with congenital anomalies (Blais L et al. J Allergy Clin Immunol. 2009;124[6]:1229-34) suggest that disease severity may be a confounder in these associations. The diagnosis of asthma, the use of other concurrent medications, and medication compliance may all be potential confounders. ICS use in pregnancy was associated with endocrine and metabolic disturbances in the offspring in a national cohort (Tegtehoff M et al. Am J Respir Crit Care Med. 2012;185[5]:557-63). However, this study did not report on systemic steroid use, asthma severity, or details of these disturbances. In summary, ICS use remains justifiable in pregnancy (Smy L et al. Can Fam Physician. 2014;60[9]:809-12) as the risk of untreated or poorly treated asthma outweighs the possible risk of ICS use, especially when alternative drugs such as systemic steroids are not without risk. Ultimately, it should be stressed that asthma control is the goal of treatment. This should be achieved with close interaction between the pregnant woman and her health-care provider.

**Registration is now open for CHEST Board Review 2017**

Looking for in-person board review prep? Join us in Orlando, August 18 to 27, for the best live review of pulmonary, critical care, and sleep medicine.

CHEST Board Review courses emphasize the same content as the ABIM and feature smaller tutorial sessions focusing on key topics, assessment tools that measure exam readiness, Mechanical Ventilation and ABIM SEP Module add-on sessions, and faculty and CHEST leadership networking opportu-

nities.

Register by March 31 and save $100. Registration can be done at http://boardreview.chest-net.org.
Dear Clot,

You really don’t take my breath away.

The EKOS® System quickly improves right ventricular function and pulmonary artery pressure.¹

EKOS® does much more than the current standard of PE care. It speeds time to dissolution by unwinding the clot’s fibrin structure, allowing greater lytic dispersion and accelerated absorption.² It also minimizes bleeding risk, requiring up to 4x less drug dosage than systemic delivery.³,⁴

Visit www.ekoscorp.com to learn more about the only endovascular device cleared by the FDA for the treatment of pulmonary embolism.

¹ In the Seattle II study of 150 patients with massive or submassive PE using an EKOS® and lytic combination, the mean RV/LV ratio decreased from 1.55 pre-procedure to 1.13 at 48 hours post-procedure (P<0.0001) while PA systolic pressure decreased from 51.4mmHg to 36.9mmHg (P<0.0001).

FDA CLEARED INDICATIONS: The EkoSonic® Endovascular System is indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries. Instructions for use, including warnings, precautions, potential complications, and contraindications can be found at www.ekoscorp.com. Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician. THE CE MARK (CE0086) HAS BEEN AFFIXED TO THE EKOSONIC® PRODUCT WITH THE FOLLOWING INDICATIONS:

Pulmonary Embolism: The EKOS EkoSonic® Endovascular System is intended for the treatment of pulmonary embolism patients with ≥50% clot burden in one or both main pulmonary arteries or lobar pulmonary arteries, and evidence of right heart dysfunction based on right heart pressures (mean pulmonary artery pressure ≥25mmHg) or echocardiographic evaluation.

EKOS and EkoSonic are registered trademarks of EKOS Corporation, a BTG International group company. “Acoustic pulse thrombolysis” is a trademark of EKOS Corporation. BTG and the BTG roundel logo are registered trademarks of BTG International Ltd in US, EU, and certain other territories and trademarks of BTG International Ltd elsewhere. © 2016 EKOS Corporation. NA-EKO-2016-0578

CHPH_60.indd   1 8/29/2016   1:56:04 PM