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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

ROBERTO BADAGLIACCA, MD, PHD

Right heart catheterization allows only an indirect description of RV function, according to Dr. Badagliacca (center).

ECHO, exercise testing reflect PAH prognosis

BY M. ALEXANDER OTTO
Frontline Medical News

FROM CHEST

Adding echocardiography and cardiopulmonary exercise testing to baseline right heart catheterization improves prognostic accuracy in idiopathic pulmonary arterial hypertension, according to a prospective Italian study of 102 newly diagnosed patients.

A combination of low right ventricular fractional area change (RVFAC) on echocardiography and low oxygen pulse on cardiopulmonary exercise testing (CPET) "identifies patients at a particularly high risk of clinical deterioration." Both are markers of right ventricular (RV) function, which is a major determinant of outcome in idiopathic pulmonary arterial hypertension [iPAH], said investigators led by Roberto Badagliacca, MD, of the Sapienza University of Rome (Chest. 2016 Aug 20. pii: S0012-3692(16)56052-8. doi: 10.1016/j.chest.2016.07.036).

PAH diagnosis requires right heart catheterization, and findings have long been known to predict PAH outcome. However, catheterization allows only "an indirect description of RV function," the investigators said. Recent studies have shown that RV echocardiography and CPET improve the accuracy of heart failure prognosis, so the investiga-

See **PAH** • *page 6*

GOLD uncouples spirometry from ABCD algorithm

Guidance gives symptoms more weight

BY M. ALEXANDER OTTO
Frontline Medical News

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has uncoupled spirometry results from the ABCD treatment algorithm; this move marks the organization's first announcement of major COPD guidance since 2011.

Spirometry now stands apart from GOLD's ABCD symptom/exacerbation risk score with its own grade, with possibilities ranging from 1 to 4. A forced expiratory volume in 1 second (FEV_1) of 80% or more of the predicted value rates a 1; the score degrades to 4 with an FEV_1 below 30%.

GOLD had been moving toward symptoms and exacerbations to guide treatment for several years before formalizing the break from spirometry in its Nov. 16 report.

"In previous GOLD documents, recommendations for management of COPD were based solely on spirometric category. However, there is considerable evidence that the level of FEV_1 is a poor descriptor of disease status, and, for this reason, the management of stable COPD based on …

See **GOLD** • *page 4*

INSIDE

Blood pressure rose after CPAP halt

BY JIM KLING
Frontline Medical News

FROM CHEST

Continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA) has a significant beneficial effect on blood pressure, according to an analysis of participants in three randomized controlled trials.

Previous meta-analyses suggested that CPAP treatment led to an average of improvement of 2-3 mm Hg, but the estimates relied on heterogeneous trials that often had low levels of CPAP adherence, and those factors might have led to an underestimation of the treatment effect. The new analysis showed that halting CPAP increases blood pressure between 5.0 and 9.0 mm Hg, compared with patients who continued using CPAP (Chest. 2016;150[6]:1202-10).

To get around the problem of adherence, researchers led by Malcolm Kohler, MD, at University Hospital of Zürich analyzed the results of three previous studies looking at the effects

See **Blood Pressure** • *page 7*

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- **Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[2,3]**
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006[2,4]**
- Safety and efficacy were evaluated in three phase 3, double-blind, placebo-controlled, multicenter trials in 1247 patients randomized to receive Esbriet (n=623) or placebo (n=624)[2]

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  - —eg, elevated liver enzymes, gastrointestinal events, and photosensitivity reactions or rash

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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, randomized, double-blind, placebo-controlled, multicenter trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and $\%DL_{co}$ (percent predicted diffusing capacity of lung for carbon monoxide) between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52. In CAPACITY 006, 344 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo. Eligible patients had %FVC ≥50% and $\%DL_{co}$ ≥35%. The primary endpoint was change in %FVC from baseline to week 72.

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

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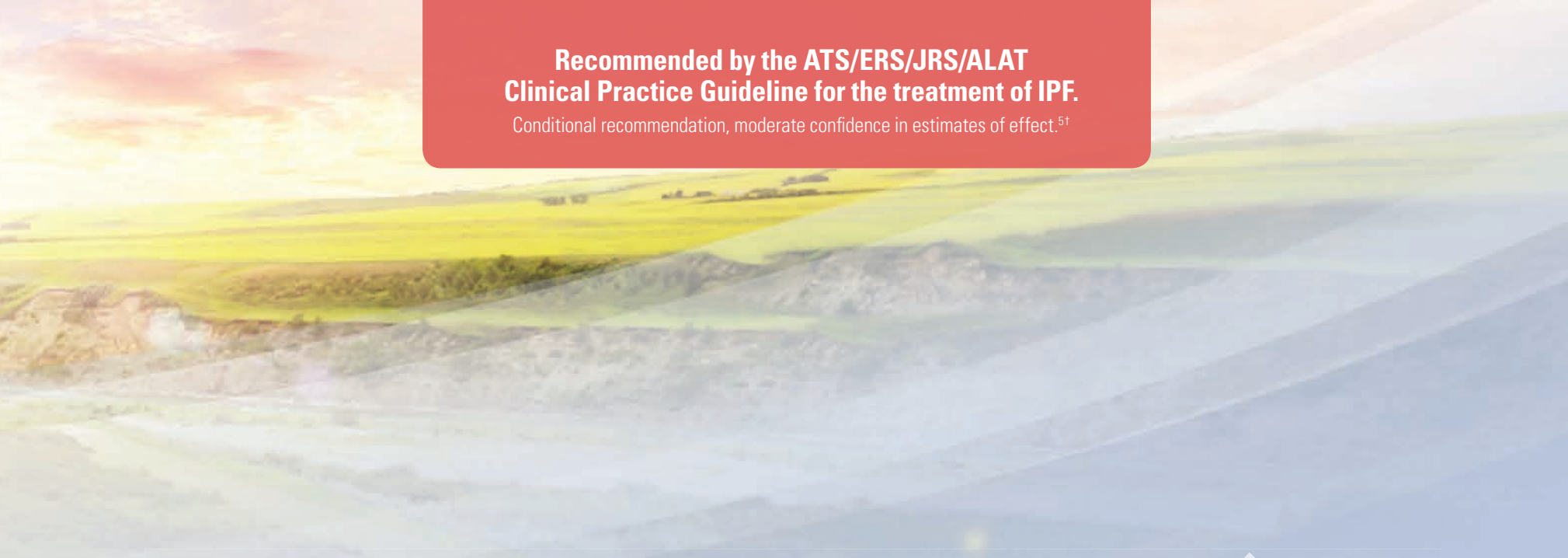

Recommended by the ATS/ERS/JRS/ALAT Clinical Practice Guideline for the treatment of IPF.

Conditional recommendation, moderate confidence in estimates of effect.[5†]

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

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

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

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

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

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

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

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

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

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

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

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

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Symptoms can guide treatment

GOLD *from page 1*

disease impact (determined mainly by symptom burden and activity limitation) and future risk of disease progression (especially of exacerbations) is recommended. ... ABCD groups are now proposed to be derived exclusively from patient symptoms and their history of exacerbations," GOLD said.

The clear focus on symptoms and exacerbations is "the major accomplishment" of the new report, which has been downloaded more than 45,000 times since it's release, a testament to GOLD's importance to clinicians trying to help COPD patients.

"We are trying to do a better job of personalizing treatment," said GOLD board member Gerard Criner, MD, FCCP, chair and professor of thoracic medicine and surgery at Temple University in Philadelphia.

The change "allows you to plan treatment based on symptoms [even] if you don't have immediate access to spirometry, and then refine treatment once you have spirometry results. It also allows you to escalate and

deescalate treatment because you are not boxed into a letter grade group" forced by spirometry. "You can also take a better look at pharmacologic versus nonpharmacologic therapy" when deciding what to do, he said.

In short, "we think it gives more freedom" to manage patients based on what seems best, Dr. Criner said.

The change allows you to plan treatment based on symptoms and then refine treatment once you have spirometry results, Dr. Criner noted.

GOLD included an example of how the new assessment can help. "Consider two patients," it said, both with an FEV_1 less than 30% and a COPD Assessment Test result of 18, but one with no exacerbations in the past year and the other with three. Both would have scored a GOLD D in the old system, and been treated similarly.

"However, with the new proposed scheme, the subject with three exacerbations ... would be labeled GOLD [spirometry] grade 4, group D," and their treatment would focus on exacerbations. The no-exacerbation patient would be classified as GOLD grade 4, group B. Treatment would focus on symptoms. Drugs are still an option, but also lung volume reduction and lung transplant, GOLD said. Spirometry, in other words, is less important than how the patient is doing.


FRONTLINE MEDICAL NEWS

Dr. Gerard J. Criner

The group incorporated "every major study up to the first week of November" in the new report, Dr. Criner said, so there's more to consider.

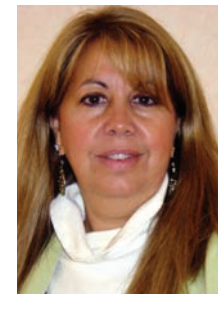
For instance, it's clear now that patients benefit from home oxygen if they are severely hypoxemic while sitting on the couch watching TV, but not if they desaturate only when they get up and walk around, or come into the clinic to exercise. "We did not" know that in 2011, he said.

GOLD also recommended pulmonary rehabilitation and palliative care when indicated, as well as ongoing evaluation to make sure patients are

Continued on following page

VIEW ON THE NEWS

Vera De Palo, MD, FCCP, comments: As health care moves toward individualized care plans for patients, the updated GOLD recommendations enhance the possibility of personalized COPD treatment. This means more symptom-focused treatment for patients and, as Dr. Criner points out, more freedom for providers to manage patients based on what seems best.



Continued from previous page

able to use their inhalers, a major problem in COPD.

GOLD said that group A patients - those with few symptoms and low exacerbation risk - should be offered a bronchodilator. Initial therapy for group B - more symptoms, but low exacerbation risk - and group C - higher exacerbation risk but fewer symptoms - "should consist of a single long-acting bronchodilator. There is no evidence to recommend one class of long-acting bronchodilator over another."

The guidance "allows you to escalate and deescalate treatment because you are not boxed into a letter grade group" forced by spirometry ... "[We] think it gives more freedom," Dr. Criner noted.

For group D - highly symptomatic with frequent exacerbations - "we recommend starting therapy with a [long-acting beta-2 agonist]/[long-acting antimuscarinic antagonist] combination," the group said.

There was no industry involvement in GOLD's report, but numerous authors and board members had pharmaceutical company ties, and GOLD's treatment advice relies on drug company studies. Dr. Criner reported personal payments from Holaria, and research funding and other nonpersonal payments from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Johnson and Johnson, and others.

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RVFAC outperformed other metrics

PAH *from page 1*

tors wanted to see if they'd do the same for PAH.

The results "strongly suggest that noninvasive measurements related to RV function obtained by combining resting echocardiography and CPET are of added value to right heart catheterization in the assessment of severity and prognostication of PAH," the researchers said.

During a mean follow-up of 528 days, 54 patients (53%) had clinical worsening, defined as a 15% reduction in 6-minute walk distance from baseline plus a worsening of functional class, nonelective PAH hospitalization, or death.

Baseline functional class and cardiac index proved to be independent predictors of clinical worsening. Adding echocardiographic and CPET variables independently improved prognostic power (area under the curve, 0.81 vs. 0.66; $P = .005$).

Compared with patients with high RVFAC and high oxygen pulse at baseline, patients with low RVFAC and low oxygen pulse had a 99.8 increase in the hazard ratio for clinical worsening, and those with high RVFAC and low oxygen had a 29.4 increase ($P = .0001$).

Several echocardiographic variables for RV function have previously been reported as independent predictors of PAH outcome. "The new finding here is that RVFAC outperformed other echocardiographic indices of systolic function," the investigators wrote.

"As for peak oxygen pulse, this variable is thought to assess maximum [stroke volume]," assumed to be determined by RV function; MRI-determined stroke volume has been previously shown to be an important predictor of survival in PAH," they said.

The mean age in the study was 52 years, mean functional class was 2.7, and mean 6-minute walk distance was 430 m; 62 subjects were women. The most relevant comorbidities were diabetes in 5 patients, hypercholesterolemia in 10, thyroid diseases in 6, and clinical depression in 7.

Patients with severe tricuspid regurgitation or exercise-induced opening of the foramen ovale were excluded. However, a reanalysis including patients with exercise-induced right to left shunting showed the same independent predictors of PAH outcome.

After diagnosis, patients were treated with endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids.

Dr. Badagliacca reported speaker and adviser fees from United Therapeutics, Dompe, GSK, and Bayer. His colleagues reported no conflicts of interest.

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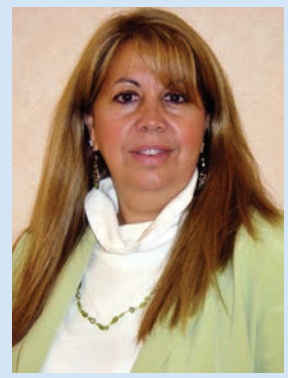

Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

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Adaptive servo ventilation cuts atrial fib burden

BY MITCHEL L. ZOLER
Frontline Medical News

ORLANDO – Adaptive servo ventilation produced a significant and clinically meaningful reduction in atrial fibrillation burden in patients with heart failure and sleep apnea in results from an exploratory, prospective, randomized study with 35 patients.

Adaptive servo ventilation (ASV) "may be an effective antiarrhythmic treatment producing a significant reduction in atrial fibrillation without clear evidence of being proarrhythmogenic," Jonathan P. Piccini, MD, said at the annual scientific meeting of the Heart Failure Society of America. "Given the potential importance of this finding further studies should validate and quantify the efficacy of ASV for reducing atrial fibrillation in patients with or without heart failure." This is "the first time" the arrhythmia effects of a sleep apnea intervention, in this case ASV, was studied in a prospective, randomized way while using implanted devices to measure the antiarrhythmic effect of the treatment, said Dr. Piccini, an electrophysiologist at Duke University in Durham, N.C., in an interview.

The new finding means that additional, larger studies are now needed, he said.

The CAT-HF (Cardiovascular Improvements With Minute Ventilation-Targeted ASV Therapy in Heart Failure) trial was originally designed to randomize 215 heart failure patients with sleep disordered breathing – and who were hospitalized for heart failure – to optimal medical therapy with or without ASV at any of 15 centers in the United States and Germany. But in August 2015, results from the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure) trial, which generally had a similar design to CAT-HF, showed an unexpected danger from ASV in patients with central sleep apnea and heart failure with reduced ejection fraction (N Engl J Med. 2015 Sept 17;373[12]:1095-105). In SERVE-HF, ASV was associated with significant increases in all-cause and cardiovascular mortality. As a result, enrollment into CAT-HF stopped prematurely with just 126 patients entered, and ASV treatment of patients already enrolled came to a halt.

The primary endpoint in the underpowered and shortened CAT-HF study, survival without cardiovascular hospitalization and with improved functional capacity measured on a 6-minute walk test, showed similar outcomes in both the ASV and control arms. But in a prespecified subgroup analysis by baseline ejection fraction, the 24 patients with heart failure with preserved ejection fraction (19% of the CAT-HF enrollment) showed a statistically significant, 62% relative improvement in the primary endpoint linked with ASV treatment compared with similar patients who did not receive ASV, Christopher M. O'Connor, MD, professor of medicine at Duke University, reported in May 2016 at the European Heart Failure meeting in Florence.

Dr. Piccini's report focused on a prespecified subgroup analysis of CAT-HF designed to examine the impact of ASV on arrhythmias. Assessment of the impact of ASV on atrial fibrillation was possible in 35 of the 126 patients in CAT-HF who had an implanted cardiac device (pacemaker, defibrillator, or cardiac resynchronization device) with an atrial lead, and assessment of ventricular arrhythmias occurred in 46 of the CAT-HF patients with an implanted high-voltage device (a defibrillator or resynchronization device) that allowed monitoring of ventricular arrhythmias.

For the atrial fibrillation analysis, the 35 patients averaged 60 years of age, and about 90% had a reduced ejection fraction. About two-thirds had an apnea-hypopnea index greater than 30.

The results showed that the 19 patients randomized to receive ASV had an average atrial fibrillation burden of 30% at baseline that dropped to 14% after 6 months of treatment. In contrast, the 16 patients in the control arm had a AF burden of 6% at baseline and 8% after 6 months. The between-group difference for change in AF burden was statistically significant, Dr. Piccini reported, with a burden that decreased by a relative 21% with ASV treatment and increased by a relative 31% in the control arm. Analysis of the ventricular arrhythmia subgroup showed that ASV had no statistically significant impact for either lowering or raising ventricular tachyarrhythmias or fibrillations.

The CAT-HF trial was funded by ResMed, a company that markets adaptive servo ventilation equipment. Dr. Piccini has received research support from ResMed and from Janssen, Gilead, St. Jude, Spectranetics, and he has been a consultant to Janssen, Spectranetics, Medtronic, GSK and BMS-Pfizer. Dr. O'Connor has been a consultant to ResMed and to several other drug and device companies.

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VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: A small prespecified subgroup of patients in the CAT-HF (Cardiovascuar improvements with minute ventilation-targeted ASV therapy in heart failure) trial randomized to adaptive servo ventilation (ASV) showed a 21% relative reduction in atrial fibrillation burden as compared to the control arm which had only 31% relative reduction. While the CAT-HF study was discontinued following results of SERVE-HF trial, this subgroup analysis included 35 patients (19 ASV arm; 16 control arm), the majority of whom had a reduced ejection fraction. This report poses interesting questions about effects of ASV on atrial fibrillation burden in those with reduced EF given the finding that central sleep apnea and Cheyne-Stokes respiration are shown to be associated with incident atrial fibrillation in older men (May et al. Am J Respir Crit Care Med 2016).

Established CPAP users studied

Blood Pressure *from page 1*

of CPAP withdrawal. The analysis included 153 OSA patients on CPAP therapy, who had been randomized to continue therapy or to withdraw from therapy for 2 weeks. Eighty-seven of these patients discontinued CPAP, and the remaining 66 patients continued the therapy. Blood pressure was measured at home and in hospital.

On average, those who discontinued CPAP had an increase in office systolic blood pressure of 5.4 mm Hg (95% confidence interval, 1.8-8.9 mm Hg; $P = .003$) and an increase in home systolic blood pressure of 9.0 mm Hg (95% CI, 5.7-12.3 mm Hg; *P* less than .001), compared with patients who continued CPAP. The effects of stopping CPAP, instead of continuing the therapy, on office diastolic blood pressure and home diastolic pressure were increases of 5.0 mm Hg (95% CI, 2.7-7.3 mm Hg; *P* less than .001) and 7.8 mm Hg (95% CI, 5.6-10.0 mm Hg; *P* less than .001), respectively.

Patients who discontinued CPAP also experienced a significant increase in apnea-hypopnea index, from 2.8/h to 33.2/h, while those who continued using CPAP, on average, experienced only a 0.3/h increase in apnea-hypopnea index from baseline.

"One clinical implication is that if you do not need to stop CPAP for obstructive sleep apnea, do not stop it. This study also suggests the importance of monitoring your blood pressure in a home setting, under usual conditions," summed up Robert Kloner, MD, PhD, director of the Huntington Medical Research Institutes Cardiovascular Research Lab, Pasadena, Calif., who was not involved in the study.

Previous studies of CPAP, such as the SAVE study published in the New England Journal of Medicine in September (N Engl J Med. 2016;375:919-31), often find little or no connection between CPAP therapy and cardiovascular outcomes. That is probably because of inadequate adherence to CPAP therapy. "That's always been the bane of sleep apnea studies," said Krishna M. Sundar, MD, FCCP, who also did not participate in the study.

The current work got around the problem by looking at patients who had already established use of CPAP. "This is a very good study," said Dr. Sundar, who is the medical director of the Sleep-Wake Center at the University of Utah, Salt Lake City.

The study was funded by the Swiss National Science Foundation and the University of Zürich. The analysis' authors and the outside experts quoted in this story reported no financial disclosures.

Failure of AEC2s implicated in pulmonary fibrosis

BY MARY ANN MOON
Frontline Medical News

The failure of type 2 alveolar epithelial cells (AEC2s), which are critical to the repair and regeneration of lung tissue, appears to be a major cause of pulmonary fibrosis, according to a report published online in Nature Medicine.

Researchers performed a series of in vitro and murine studies to better understand the molecular mechanisms underlying pulmonary fibrosis, which is believed to result from repeated microinjuries to the alveolar epithelium that in turn promote excessive, sustained fibroblast activation with matrix-producing myofibroblasts. They found that expression of both hyaluronan (HA) and Toll-like receptor 4 (TLR4) on AEC2s is deficient in a mouse model of pulmonary fibrosis and in samples of lung tissue from patients with the disease, but not in samples from healthy control subjects or from patients with chronic obstructive pulmonary disease (COPD).

"The main finding here is that the endogenous matrix glycosaminoglycan HA and the innate immune receptor TLR4 are required for optimal AEC2 renewal and for limiting fibrosis after lung injury," said Carol Liang, MD, of the department of medicine and the Women's Guild Lung Institute, Cedars-Sinai Medical Center, Los Angeles, and her associates.

"These findings are the first published evidence that pulmonary fibrosis is primarily a disease of AEC2 stem cell failure," Dr. Liang said, in a written statement.

"The main finding here is that the endogenous matrix glycosaminoglycan HA and the innate immune receptor TLR4 are required for optimal AEC2 renewal and for limiting fibrosis after lung injury," Dr. Liang said.

The investigators began by showing that AEC2s engineered to stop expressing hyaluronan or TLR4 (by deleting the genes that encode for that expression) showed impaired self-renewal in vitro, compared with normal AEC2s. In a mouse model, the engineered AEC2s also caused impairment in the healing of deliberately induced lung injury.

In addition, the researchers developed a mouse model of pulmonary fibrosis and showed that treatment with exogenous interleukin 6 "enhanced AEC2 renewal and partially reversed the fibrotic phenotype" in vivo.

"To determine whether our observations in the mouse model of [deficient] AEC2s have relevance to human disease, we isolated AEC2s from lung explants of human subjects who had undergone lung transplantation because of [idiopathic pulmonary fibrosis]," the researchers said. These samples showed marked depletion in the number of AEC2s, compared with samples taken from healthy control subjects and from patients with COPD.

In addition, the few remaining AEC2s in the samples affected by pulmonary fibrosis were deficient in the expression of HA, compared with those in the samples from control subjects. This suggests that loss of cell-surface HA is unique to severe pulmonary fibrosis, the researchers said (Nature Med. 2016. doi: 10.1038/nm.4192).

Since pulmonary fibrosis is characterized by patchy areas of parenchymal fibrosis alternating with relatively normal lung tissue, the investigators then compared AEC2s taken from these two distinct types of tissue in the patient group. They found that AEC2 cells from affected areas of the lung showed much more markedly reduced expression of HA than those from healthy areas of the lung. Flow cytometry testing further demonstrated that the number of AEC2s also was greatly reduced in affected lung tissue but relatively higher in more normal lung tissue. However, even the "healthy" lung tissue from affected patients had lower numbers of AEC2s and impaired cell renewal when compared with tissue from unaffected control subjects, the researchers noted.

"In future studies, we will explore how the loss of hyaluronan promotes fibrosis and how it might be restored to cell surfaces. These endeavors could lead to new therapeutic approaches" for this progressive, fatal disease for which there is no effective treatment at present, Dr. Liang said, in the written statement.

Severe post-thoracotomy pain predicts persistent postop pain

BY DEEPAK CHITNIS
Frontline Medical News

Patients who suffer from severe pain in the days immediately following an open thoracotomy are significantly more likely to still be experiencing pain from the procedure 6 months later, according to a study published in the Journal of Clinical Anesthesia.

"A recognized cause of persistent postsurgical pain is poorly controlled immediate postoperative pain," wrote the authors, led by Gopinath Niraj, MD, of the University Hospitals of Leicester (England) NHS Trust. "Open thoracotomy can induce significant pain during the immediate postoperative period. Patients undergoing thoracotomy also have one of the greatest incidences of chronic postoperative pain and disability among all the surgical procedures."

The researchers gave a questionnaire to 504 patients who underwent open thoracotomy at a single center between May 2010 and April 2012. They asked yes/no questions about the existence of and location of postoperative pain, and numerical questions regarding the severity of pain. Scores of 7 or higher on a 10-point scale indicated "severe pain," according to the investigators (J Clin Anesth. 2017;36:174-7). Subjects were evaluated at 72 hours and at 6 months after the operation.

Of the 504 patients, there were 364 survivors, of which 306 received questionnaires. Of those 306, 133 (43%) reported at least five incidents of severe pain within 72 hours of undergoing the operation. Within this group, 109 (82%) reported feeling some amount of persistent pain 6 months later. Chronic post-thoracotomy pain was considered severe in 10% of those subjects, while 24% reported it as moderate and 48% said it was mild. A total of 289 of the 306 subjects (95%) received an epidural analgesic in the 72 hours after thoracotomy. Pain management was rated excellent by 36.3%, good by 43.8%, fair by 15.8%, and poor by 3.8%. of patients.

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Two factors associated with vocal cord dysfunction in study

BY DOUG BRUNK
Frontline Medical News

AT CHEST 2016

LOS ANGELES – Female sex and the absence of wheezing were the only factors significantly associated with vocal cord dysfunction in patients with high pretest probability of disease, a retrospective analysis showed.

The findings differ from those of the Pittsburgh Vocal Cord Index, which identified symptoms of throat tightness, dysphonia, absence of wheezing, and the presence of odors as key features predictive of vocal cord dysfunction (VCD). "This proves the point that VCD is an elusive diagnosis," lead study author Phalgoon Shah, MD, said, in an interview, at the annual meeting of the American College of Chest Physicians. "If you have a high rate of clinical suspicion, you don't have to do a laryngoscopy. Send them for speech therapy. If they get better, they have VCD."

Of 244 patients who Dr. Shah and his colleagues retrospectively evaluated, 136 (56%) were diagnosed with VCD; the remaining 108 (44%) were not. As many as 66% of females had a diagnosis of VCD, compared with 48% of males ($P = .006$) The percentage of patients with VCD who had an absence of wheezing was 49% ($P = .037$).

Depression, anxiety, throat tightness, dysphonia, odor symptom trigger, lack of response to bronchodilator or truncation, and flattening of the inspiratory volume curve did not predict VCD.

The patients were active duty military personnel and veterans who were referred to the pulmonary function lab at Tripler Army Medical Center, Honolulu, for suspected VCD between 2010 and 2014. The researchers identified patients by laryngoscopy procedure code and collected numerous variables, including demographic information, past medical history, pulmonary function test data, and clinical variables such as ED visits for dyspnea. "For the first time, we are saying that exercise laryngoscopy is not the gold standard," said Dr. Shah of the division of pulmonary and critical care at Tripler.

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‘Stepping’ up robotic lobectomy instruction

BY RICHARD MARK KIRKNER
Frontline Medical News

Teaching minimally invasive robotic surgery to residents can be difficult in a health care environment obsessed with quality outcome measures and under scrutiny by hospital administrators and payers, but researchers at the University of Alabama at Birmingham may have devised a method to instruct residents in robotic lobectomy without compromising patient outcomes, according to a study published in the October issue of the Journal of Thoracic and Cardiovascular Surgery (2016;152:991-7).


DR. CERFOLIO

Robert J. Cerfolio, MD, MBA, FCCP, and his coauthors divided the procedure into 19 sequential, teachable steps and allowed residents to perform selected steps during operations that Dr. Cerfolio directed.

“We then applied simulation training, coaching techniques, and video review of each step to help improve the steps that residents could not complete,” Dr. Cerfolio and his coauthors said.

Surgeons in academic centers face the challenge of teaching “the art and science of surgery,” Dr. Cerfolio and his colleagues said, while maintaining quality outcomes. “Teaching minimally invasive surgery, especially robotic surgery, is challenging given the risks and the limited availability of the robot.”

The researchers acknowledged that other groups have taken a similar approach to training, but this is the first study that included video review, coaching, and instruction tied to time constraints, they said.

“A major concern is that while teaching robotic surgery, patients can be injured, care is worse, and metrics that are increasingly used as surrogates for quality outcomes suffer,” they noted.

They allotted each step in the procedure a set amount of time in which the resident had to complete it, totaling 80 minutes for all 19 steps and ranging from 1 minute to inspect the pleura after placing ports (9 minutes) to 20 minutes to close the five incisions. If the resident completed the task in the allotted time, it was recorded as “performed.”

Between February 2010 and December 2010 Dr. Cerfolio performed 520 robotic lobectomies, and over time the percentage of successful steps per resident improved.

For example, in the first year, 50% of thoracic surgery residents completed the first five steps (mark and place ports, inspect pleura, resect the inferior pulmonary ligament, and remove three lymph nodes), but by the last year of the study 90% of them successfully completed the five steps.

Dr. Cerfolio and coauthors acknowledged “many flaws” in their study, but the study also had strengths: It involved only one operation and corroborated the database with each resident’s own surgical logs.

“Operations such as robotic lobectomy can be successfully taught by dividing them into a series of surgical steps and coaching each step,” they noted. Recording what residents can and can’t do, reviewing video, and coaching contribute to the process to improve their skills. “Further studies that scientifically measure ‘ways to teach’ and ways to coach and mentor are needed,” they said.

Dr. Cerfolio disclosed relationships with Intuitive Surgical, Ethicon, Community Health Services, KCL, Bovie and C-SATS. Coauthor Douglas Minnich, MD, is a consultant to Medtronic. The other co-authors had no financial relationships to disclose.

VIEW ON THE NEWS

Francis J. Podbielski, MD, FCCP, comments: This in an interesting and clinically relevant study given the emphasis many institutions have placed on becoming “robotic” centers of excellence. The overall cost effectiveness of robotic surgery from a public policy standpoint remains a matter of intense study given the scarcity of resources in many health-care settings.

REBOA may be thoracotomy alternative in traumatic arrest

BY JESSICA CRAIG
Frontline Medical News

WASHINGTON – Resuscitative endovascular balloon occlusion of the aorta (REBOA) could be an acceptable alternative to thoracotomy in traumatic arrest patients who are hemorrhaging below the diaphragm, according to the results of a small pilot study which were presented by William Teeter, MD, at the annual clinical congress of the American College of Surgeons.

Furthermore, virtual simulation training sufficiently prepares surgeons to safely use the REBOA technique in the acute care setting, a separate study found. Importantly, this training has the potential to allow REBOA to become a widespread tool for surgeons regardless of their endovascular surgical experience.

REBOA is an emerging and less invasive method of aortic occlusion during traumatic arrest. “Recent evidence published in the Journal of Trauma suggests that REBOA has similar outcomes to resuscitative thoracotomy with aortic cross-clamping or RTACC,” said Dr. Teeter, who is currently an emergency medicine resident at the University of North Carolina, Chapel Hill, but conducted this research during a fellowship at the University of Maryland Medical Center’s R Adams Cowley Shock Trauma Center in Baltimore.

Dr. Teeter presented the preliminary results of a pilot study involving 19 patients who received RTACC between 2008 and 2013 and 17 patients who received REBOA between 2013 and 2015. All study participants were trauma patients who arrived at the R Adams Cowley Shock Trauma Center in arrest or arrested shortly after arrival.

Age, gender, Glasgow Coma Scale, and injury severity score were the same or similar between the two groups, Dr. Teeter reported. Mean systolic blood pressure at admission was 14 mmHg for the REBOA group and 28 mmHg for the RTACC group; however, the majority of patients (82% of REBOA patients and 73% of RTACC patients) arrived with a blood pressure of 0, reported Dr. Teeter.

“At our center there has been a marked change in practice regarding which patients receive resuscitative thoracotomy and which get REBOA,” said Dr. William Teeter.

Importantly, patients in the RTACC group who had penetrating chest injury were excluded for this analysis, Dr. Teeter noted, adding that there was a slightly higher incidence of blunt trauma within the REBOA group likely due to “a change in practice at the trauma center during this time.”

All resuscitations were captured with real-time videography. Continuous vitals were also collected and analyzed.

While more RTACC patients survived to the operating room (53% vs. 68%), among the REBOA group there were more patients who experienced return of spontaneous circulation (53% vs. 37%). However, neither of these results was statistically significant.

Following occlusion of the aorta, the blood pressure measures, taken from continuous vital signs and averaged over a 15-minute period, were 80 mmHg for the REBOA group and 46 mmHg for the RTACC group. Again, this result was statistically insignificant but trended toward favoring REBOA.

Overall, patient survival was dismal. Only one patient who received REBOA survived.

Following Dr. Teeter’s presentation, the study’s assigned discussant, Nicole A. Stassen, MD, of the University of Rochester Medical Center, N.Y., noted that while post-occlusion blood pressure was higher for the REBOA group it seemed not to matter as the majority of patients did not survive. Dr. Stassen also asked if these preliminary results were sufficient to inform or change clinical practice.

In response, Dr. Teeter explained that the pilot study was conducted at a time when the literature was unclear about how patients would respond to open versus endovascular occlusion, and this data helped guide further research and resuscitation efforts.

“At our center there has been a marked change in practice regarding which patients receive resuscitative thoracotomy and which get REBOA,” he added and concluded that “these and previous data

Continued on page 16

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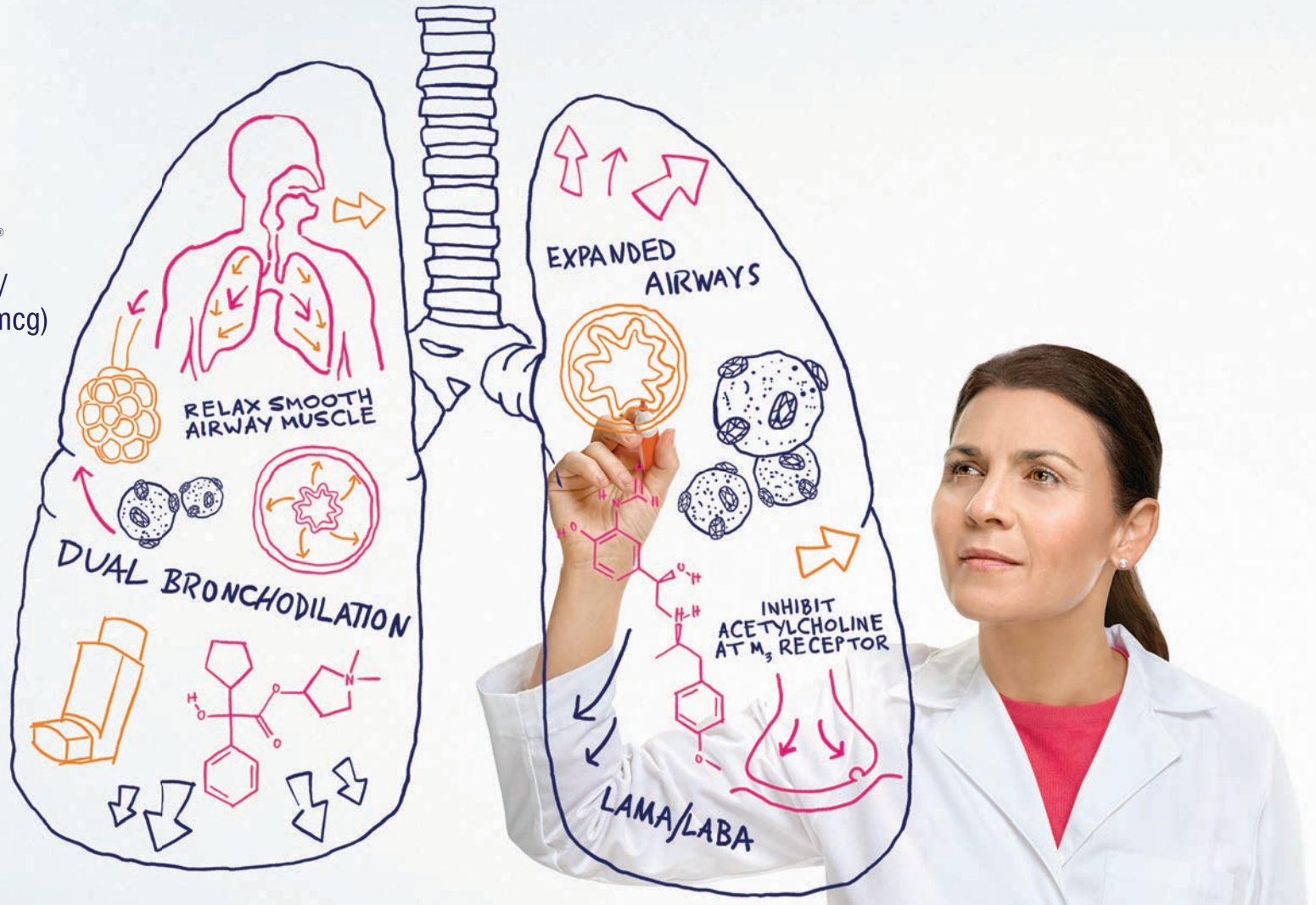

BEVESPI AEROSPHERE is indicated for the maintenance treatment of COPD.

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

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting $beta_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

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

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

WARNINGS AND PRECAUTIONS

- BEVESPI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition
- BEVESPI should not be used for the relief of acute symptoms (ie, as rescue therapy for the treatment of acute episodes of bronchospasm). Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist
- BEVESPI should not be used more often or at higher doses than recommended, or with other LABAs, as an overdose may result
- If paradoxical bronchospasm occurs, discontinue BEVESPI immediately and institute alternative therapy
- If immediate hypersensitivity reactions, including angioedema, urticaria, or skin rash, occur, discontinue BEVESPI at once and consider alternative treatment
- BEVESPI can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, blood pressure, or symptoms. If such effects occur, BEVESPI may need to be discontinued
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Be alert to hypokalemia and hyperglycemia
- Worsening of narrow-angle glaucoma or urinary retention may occur. Use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur

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

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Adverse reactions with BEVESPI AEROSPHERE with a ≥2% incidence and more common than placebo were urinary tract infection and cough.[1]

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

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

†Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials.[1-3]

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

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore BEVESPI should be used with extreme caution in patients being treated with these agents
- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-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 FEV_1 at Week 24 for BEVESPI AEROSPHERE compared with placebo (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; $P<0.0001$ for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,3]

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

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABAs) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

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

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

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

Deterioration of Disease and Acute Episodes

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

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should also prescribe an inhaled, short acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

Excessive Use of BEVESPI and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled medicines containing beta$_2$-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason *[see Drug Interactions (7.1) in the full Prescribing Information]*.

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. If such effects occur, BEVESPI AEROSPHERE may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

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

Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta$_2$-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$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

The incidence of adverse reactions with BEVESPI AEROSPHERE in Table 1 is based on reports in two 24-week, placebo-controlled trials (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 51% (range: 19% to 82%) and the mean percent reversibility was 20% (range: -32% to 135%).

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of $beta_2$ adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

Non-Potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by $beta_2$-agonists, especially when the recommended dose of the $beta_2$-agonist is exceeded. Approximately 17% of subjects were taking non-potassium sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

BEVESPI AEROSPHERE, as with other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

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

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

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

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 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 $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

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Cerebral protection in TAVI cuts ischemic lesions

BY MARY ANN MOON
Frontline Medical News

In patients undergoing transcatheter aortic valve implantation, use of a cerebral protection device to entrap and remove embolic debris reduced both the number and the size of ischemic brain lesions, according to a report published in JAMA.

The frequency and severity of post-procedure stroke symptoms were similar with and without the filter; however, the researchers noted that the study included only 100 patients and was not powered to assess differences in stroke rates.

Various cerebral protection devices were invented in response to the finding of a threefold increase in periprocedural stroke mortality following TAVI. Yet "clear evidence of the efficacy of any embolic protection device in TAVI is still missing," said Stephan Haussig, MD, of the University of Leipzig (Germany) Heart Center, and his associates.

They performed a prospective randomized clinical trial at their center to assess the efficacy of the only cerebral protection device that was available when their study was designed. For the study, 100 patients with severe, symptomatic aortic stenosis were randomly assigned to undergo TAVI either with (50 patients) or without (50 patients) the use of a protective filter to capture embolic debris. The filter device was estimated to fully protect 74% of the brain and partially protect 24%, leaving only 2% unprotected.

The primary endpoint of the study was the number of ischemic brain lesions detected on diffusion-weighted MRI in the filter group, compared with the control group. This imaging was performed at baseline, 2 days after the procedure, and 7 days after the procedure.

In protected brain regions, the median number of new ischemic brain lesions was markedly lower in the filter group than in the control group (4 vs. 10) at 2 days, as well as at 7 days (3 vs. 7, respectively). In addition, the volume of new lesions in protected brain regions also was markedly lower in the filter group at 2 days (242 mm vs. 527 mm) and at 7 days (101 mm vs. 292 mm).

It is important to note that this study wasn't powered to assess differences in stroke rates. Larger studies will need to be completed to assess the impact of protective devices on neurological and functional outcomes, according to Dr. Stephan Haussig and his associates.

Similar protective effects were evident when the entire brain was evaluated. The median number of new lesions was markedly lower in the filter group than in the control group (8 vs. 16) at 2 days and at 7 days (5 vs. 10, respectively). The median lesion volume also was markedly lower in the filter group at 2 days (466 mm vs. 800 mm) and at 7 days (205 mm vs. 720 mm).

However, this protective effect didn't translate into a substantive difference in neurologic outcomes between the two study groups, as assessed by the National Institutes of Health Stroke Scale and the modified Rankin scale. Five patients in each group developed symptoms of stroke, and all symptoms were deemed minor and nondisabling, the investigators said (JAMA 2016;316[6]:592-601).

It is important to note that this study wasn't powered to assess differences in stroke rates. Larger studies will be needed to assess the impact of protective devices on neurological and functional outcomes, Dr. Haussig and his associates wrote.

The two study groups also did not differ with regard to complications. Thirty-day mortality was 0% in the filter group and 2% in the control group, a nonsignificant difference.

The investigators pointed out that protective filter devices can protect the brain only while they are in place during TAVI, "which usually takes less than 1 hour and represents only 2% of the first 48 hours after which the first MRI was performed in this study. Based on the analyzed material captured and removed by the filters – e.g., old and fresh thrombus, endothelium, atheromatous plaque, valve tissue, and calcium – it becomes evident that causes of cerebral injury are risk does not resolve immediately at the end of the TAVI procedure," they said.

Perhaps the study's most surprising finding was that nearly every patient had new cerebral lesions consistent with infarcts, but most of these were very small and not associated with any neurocognitive or functional impairments.

This study was limited in that it involved a single cardiac team assessing only one brand of filter device at a single hospital, so the results are not necessarily generalizable to a broader patient population or to the many other devices that have since been developed, Dr. Haussig and his associates added.

This study was funded by a grant from Claret Medical and Medtronic. Dr. Haussig reported having no relevant financial disclosures; his associates reported ties to numerous industry sources.

VIEW ON THE NEWS

Hossein G. Almassi, MD, FCCP, comments: As there was no significant difference in clinical neurological outcomes related to use of a filter device, although there was significantly fewer and smaller brain lesions in the stroke group, one is left to conclude that the majority of MRI findings after TAVI are not clinically relevant. Is the added cost of a cerebral protection device cost effective given the equivalent neurological outcomes in the both groups?

Continued from page 11

suggest that the time performing thoracotomy for resuscitation purposes may be better spent performing CPR with REBOA."

At the very least, this pilot study demonstrated that "REBOA may be an acceptable alternative to RTACC." Further analysis of larger study populations will be published soon and will show that REBOA may be preferred over RTACC, according to Dr. Teeter.

In a subsequent presentation, David Hampton, MD, a surgical critical care fellow at the University of Maryland Medical Center's R Adams Cowley Shock Trauma Center, confirmed that many recent studies have demonstrated that REBOA is a comparable alternative to emergency thoracotomies. In fact, REBOA is commonly used throughout Japan, the United Kingdom, and in northern Europe; however, in the United States, REBOA is currently only used at a few Level 1 trauma centers and in the military, according to Dr. Hampton.

A major hindrance to wider-spread REBOA use in the United States is the lack of endovascular training for surgeons during residency which has resulted in a limited number of surgeons who can perform the REBOA technique and a limited number of surgeons who can teach the procedure to others, said Dr. Hampton.

In lieu of experience, formalized 1- or 2-day endovascular simulation courses, such as BEST, were created to prepare surgeons to use techniques such as REBOA. Prior validation studies, including those conducted by researchers at the University of Maryland, demonstrated that surgeons who participated in these courses improved surgical technique and increased their surgical knowledge base, Dr. Hampton reported.

To further elucidate the benefits of these training courses on the successful use of REBOA in the acute care setting, Dr. Hampton and his associates selected nine acute care surgeons with varying endovascular surgical experience to complete the 1-day BEST course and then compared surgeons' performances of the REBOA technique after successful course completion.

During the study, a total of 28 REBOA procedures were performed, 17 by the surgeons with no endovascular experience, and the remaining 11 by surgeons with endovascular surgical experience.

Overall, there was no difference in wire placements, sheath insertion, position or localization of balloons, or balloon inflation. In addition, there was no difference in mortality among patients, and there were no known REBOA complications during this study.

In conclusion, endovascular experience during residency is not a prerequisite for safe REBOA placement, Dr. Hampton commented.

Taken together, these two research studies are really helping to break ground on REBOA use in the acute care setting, commented an audience member.

The Department of Defense funded Dr. Teeter's study. Dr. Teeter and Dr. Hampton both reported having no disclosures.

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CSLap for post-esophageal surgery complications

BY RICHARD MARK KIRKNER
Frontline Medical News

Ingestion of caustic substances like alkali, acid, and bleaches that call for esophageal surgery is relatively rare, and the study of dealing with postsurgery complications even rarer, but a team of surgeons from a large public referral hospital in Paris has collected enough cases over the first years of this century to report that a form of revision surgery in these cases can yield good outcomes with acceptable morbidity, according to a study in the Journal of Thoracic and Cardiovascular Surgery (2016;152:1378-85).

Thibault Voron, MD, and coauthors at Hôpitaux Saint-Louis and the University of Paris performed revision cervicosternolaparotomy (CSLap) on 55 patients from 1999 to 2015. Two patients (4%) died and the severe morbidity rate was 27%, but the long-term functional success rate was 85%. "Of note, these figures compare favorably with results of primary esophageal reconstruction for caustic injuries in the literature," Dr. Voron and colleagues said. Overall the study authors performed revision surgery on 100 patients, with the remaining 45 undergoing repair through a limited approach. There were no significant differences in characteristics between the two groups.

Primary esophageal reconstruction for caustic injuries can usually be done at referral centers with good results, but up to half of these patients can have late complications, consisting mostly of strictures and redundancy that can cause loss of function, Dr. Voron and coauthors said. Published series have reported revision surgery in 15%-38% of patients (Dis Esophagus. 2008;21:E1-5; Dis Esophagus. 1999;12:7-9), but revision surgery itself is difficult to accomplish.

CSLap involves a large operative field from the jaw to the pubis. It starts with a comprehensive neck exploration through the previous cervical incision or with a median laparotomy to rule out a limited-approach repair. CSLap was undertaken when the graft was too short for a tension-free anastomosis. After the upper part of the graft was dissected from the thoracic inlet, the abdomen was opened for dissection of the abdominal part of the transplant. All scar tissues and strictures were excised after the transplant release, and a new anastomosis was constructed in healthy tissues. In cases involving life-threatening complications, patient survival prevailed over graft preservation and reconstruction of digestive continuity. The operations took up to 10 hours, with 8 hours, 20 minutes the median.

The researchers found 2 distinct indications for CSLap: graft strictures in 43 (78%) of patients to rescue the primary conduit and reconstruct the cervical anastomosis and a need to access the retrosternal space to treat graft-related complications. "Graft lengthening was definitely not the issue in this situation," they said of the latter indication. Four patients had emergency revision CSLap for spontaneous graft perforation and complications related to caustic reingestion.

TAVR valve durability supported in follow-up

BY MITCHEL L. ZOLER
Frontline Medical News

WASHINGTON – First-generation, balloon-expandable transcatheter aortic valves had a less than 1% rate of valve failure in planned echocardiography examinations during follow-up that extended as long as 5 years after valve placement in more than 2,400 patients, a demonstration of durability that experts uniformly called "reassuring."

This finding from patients who underwent transcatheter aortic valve replacement (TAVR) in the first U.S. pivotal trial for these devices, PARTNER 1 parts A and B, and during the subsequent continued-access program at PARTNER 1 study sites, represents the largest and longest systematic ultrasound follow-up of TAVR patients, Pamela S. Douglas, MD, said at the Transcatheter Cardiovascular Therapeutics annual meeting.

This evaluation of 2,404 TAVR patients in the PARTNER 1 trial examined by echocardiography and encompassing 6,493 patient-years of follow-up is the "largest core-lab based study of transcatheter heart valves to date. These data demonstrate excellent durability of transcatheter heart valves, suggesting that the low 5-year survival observed in this cohort is not related to adverse hemodynamics or transcatheter heart valve deterioration," said Dr. Douglas, professor of medicine at Duke University, Durham, N.C.

Her findings showed that out of the 2,482 patients treated with TAVR (and including those without echo follow-up) either in the trial or during the continued access program and followed for a median of 2.9 years and an average of 2.6 years, 20 patients (0.8%) required a reintervention. Four of these 20 patients (0.2% of the total cohort) showed a "classic pattern" of aortic valve deterioration marked by an increased valve pressure gradient and a reduced valve area, she reported.

"Reintervention was rare, became less frequent over time, and was usually not due to structural deterioration of the transcatheter heart valve," she said. But Dr. Douglas also cautioned that among the patients who received the first-generation, balloon expandable Sapien valve in this cohort, just 39% survived to 5 years, and a mere 282 patients (11%) actually underwent echocardiographic examination at 5 years.

"This is one of several steps we need to take to figure out the durability of transcatheter valves," said Jeffrey J. Popma, MD, professor of medicine and an interventional cardiologist at Beth Israel Deaconess Medical Center, Boston. He noted that data are needed from follow-up periods of 8 or 10 years, but these data will not be available until intermediate- or low-risk patients undergo TAVR in controlled circumstances and have long-term follow-up.

"Ten-year follow-up data will essentially be impossible" for the high-risk or inoperable patients treated with TAVR in the PARTNER 1 trial, which focused on the sickest patients with aortic stenosis, said Dr. Popma, lead investigator for several studies of TAVR using self-expanding aortic valves and marketed as CoreValve devices.

"We obviously need to follow patients longer. The 5-year results look terrific, and so very reassuring, but we need to keep an eye on this as we move TAVR into less sick and younger patients," said Dr. Robert O. Bonow, professor of cardiology at Northwestern University, Chicago. "Durability is the remaining frontier in terms of moving TAVR into younger patients," Dr. Bonow said at the meeting, which was sponsored by the Cardiovascular Research Foundation.

These data continue to show that "transcatheter valves have looked hemodynamically superior to surgically-placed valves with respect to the VARC (Valve Academic Research Consortium)–2 criteria" for prosthetic valve function, Dr. Popma noted.

PARTNER 1 was sponsored by Edwards Lifesciences, the company that had marketed the Sapien first-generation, balloon expandable TAVR system. Dr. Douglas has received research support from Edwards. Dr. Popma has been the lead investigator for several studies of a self-expanding TAVR system sponsored by Medtronic, and he has also received research funding from several other companies, has been a consultant to Boston Scientific and Direct Flow, and owns equity in Direct Flow. Dr. Dvir has been a consultant to and received research support from Edwards, Medtronic, and St. Jude. Dr. Reardon has been a consultant to Medtronic.

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Embolic protection cut lesions, did not aid neurocognition

BY MARY ANN MOON
Frontline Medical News

The largest randomized clinical trial to assess the safety and efficacy of cerebral embolic protection systems during transcatheter aortic valve replacement yielded puzzling and somewhat contradictory results, according to a report presented at the Transcatheter Cardiovascular Therapeutics annual meeting and published simultaneously in the Journal of the American College of Cardiology.


DR. KAPADIA

Virtually every device in this industry-sponsored study involving 363 elderly patients (mean age, 83.4 years) with severe aortic stenosis trapped particulate debris as intended, the mean volume of new lesions in the protected areas of the brain was reduced by 42%, and the number and volume of new lesions correlated with neurocognitive outcomes at 30 days.

However, the reduction in lesion volume did not achieve statistical significance, and the improvement in neurocognitive function also did not reach statistical significance.

In addition, "the sample size was clearly too low to assess clinical outcomes, and in retrospect, was also too low to evaluate follow-up MRI findings or neurocognitive outcomes." Nevertheless, the trial "provides reassuring evidence of device safety," said Samir R. Kapadia, MD, of the Cleveland Clinic (J Am Coll Cardiol. 2016 Nov 1. doi: 10.1016/j.jacc.2016.10.023).

In this prospective study, the investigators assessed patients at 17 medical centers in the United States and 2 in Germany. In addition to being elderly, the study patients were at high risk because of frequent comorbidities, including atrial fibrillation (31.7%) and prior stroke (5.8%).

In all, 121 patients were randomly assigned to undergo TAVR with a cerebral embolic protective device and 119 to TAVR without a protective device. New brain lesions were then assessed via MRI at 2-7 days post procedure, and neurocognitive function was assessed at 30 days.

VIEW ON THE NEWS

Francis J. Podbielski, MD, FCCP, comments: The authors have demonstrated the safety of cerebral protection systems, but not their clinical benefit in terms of preventing adverse neurological outcomes. As they note, a larger study group might produce a statistical difference. Commentary on the added cost of the device would be helpful to weigh their cost effectiveness.

went TAVR but not MRI in a safety arm of the trial.

The protection devices were placed "without safety concerns" in most patients. The rate of major adverse events with the device was 7.3%, markedly less than the 18.3% prespecified performance goal for this outcome. Total procedure time was lengthened by only 13 minutes when the device was used, and total fluoroscopy time was increased by only 3 minutes. These findings demonstrate the overall safety of using the device, Dr. Kapadia said.

Debris including thrombus with tissue elements, artery wall particles, calcifications, valve tissue, and foreign materials was retrieved from the filters in 99% of patients.

The mean volume of new cerebral lesions in areas of the brain protected by the device was reduced by 42%, compared with that in patients who underwent TAVR without the protection device. However, this reduction was not statistically significant, so the primary efficacy endpoint of the study was not met.

Similarly, neurocognitive testing at 30 days showed that the volume of new lesions correlated with poorer outcomes. However, the difference in neurocognitive function between the intervention group and the control group did not reach statistical significance.

The 5-day "window" for MRI assessment having been too long was among the study's limitations, Dr. Kapadia said.

Claret Medical funded the study and Dr. Kapadia's associates reported numerous ties to industry sources. The meeting was sponsored by the Cardiovascular Research Foundation.

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Indication

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

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, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with potent CYP3A4 inducers such as barbiturates, 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)

The Revatio® Family

Available in OS, tablet, and injection forms.

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

Revatio® sildenafil

PP-REV-USA-0090-01

July 2016

Revatio® sildenafil 20 mg tablets

Brief Summary of Prescribing Information. Consult Full Prescribing Information at REVATIOHCP.com

INDICATION AND USAGE

REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability 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 predominately 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.

DOSAGE 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 out 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. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on 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 constitution).

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 riociguat, 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 causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, 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 adversely 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 veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-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. This effect 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 unknown in patients with bleeding disorders or active peptic ulceration.

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: low 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 per year in 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 acute onset 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. 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.

There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

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 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 VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA 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 may 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 study (Study 1) 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 by at least 3% of REVATIO-treated patients (20 mg three times a day) and 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)

	Placebo, % (n=70)	REVATIO 20 mg three times a day, % (n=69)	Placebo-Subtracted, %
Epistaxis	1	9	8
Headache	39	46	7
Dyspepsia	7	13	6
Flushing	4	10	6
Insomnia	1	7	6
Erythema	1	6	5
Dyspnea exacerbated	3	7	4
Rhinitis	0	4	4
Diarrhea	6	9	3
Myalgia	4	7	3
Pyrexia	3	6	3
Gastritis	0	3	3
Sinusitis	0	3	3
Paresthesia	0	3	3

At doses higher than the recommended 20 mg three times a day, there was a greater incidence of some adverse reactions including flushing, diarrhea, 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, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. 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 the use of sildenafil without sexual activity. Others were reported to have occurred hours 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 CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 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 patients who experienced symptomatic 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/m^2 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/m^2 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 In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

The primary objective of the study was to assess the effect of REVATIO on exercise capacity as measured by cardiopulmonary exercise testing in pediatric patients developmentally able to perform the test (n=115). Administration of REVATIO did not result in a statistically significant improvement in exercise capacity in those patients. No patients died during the 16-week controlled study.

After completing the 16-week controlled study, a patient originally randomized to REVATIO remained on his/her dose of REVATIO or, if originally randomized to placebo, was randomized to low-, medium-, or high-dose REVATIO. After all patients completed 16 weeks of follow-up in the controlled study, the blind was broken and doses were adjusted as clinically indicated. Patients treated with sildenafil were followed for a median of 4.6 years (range 2 days to 8.6 years). During the study, there were 42 reported deaths, with 37 of these deaths reported prior to a decision to titrate subjects to a lower dosage because of a finding of increased mortality with increasing REVATIO doses. For the survival analysis which included 37 deaths, the hazard ratio for high dose compared to low dose was 3.9, p=0.007. Causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children.

Geriatric Use Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Patients with Renal Impairment No dose adjustment is required (including severe 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.

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Introducing our new Editorial Board Members

M. Patricia Rivera, MD, FCCP, is a Professor of Medicine in the Pulmonary Division, Department of Medicine at the University of North Carolina at Chapel Hill. She is a Co-Director of the Multidisciplinary Thoracic Oncology Program, and Director of the Lung Cancer Screening Program at UNC. She currently serves as Co-chair of the CHEST Thoracic Oncology NetWork and has been an editor and writer for the CHEST Lung Cancer Guidelines.

Nirmal S. Sharma, MD, is an Assistant Professor of Medicine in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Alabama at Birmingham. His clinical expertise is in the field of lung transplantation and advanced lung diseases including extracorporeal life support technologies for acute respiratory failure. His research is focused on the interaction of lung microbiome and innate immunity and its role in causing chronic rejection in lung transplantation. His other clinical interests include management of acute respiratory distress syndrome, pulmonary embolism, and lung donor management.

This month in *CHEST*: Editor's picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Editor in Chief, CHEST

Editorial

Spread the Word About *CHEST* for 2017: Collaboration With Elsevier, Publishing of Guidelines, More Multimedia Content, and Changes for Reviewers and Authors. By Dr. Richard S. Irwin; Dr. John E. Heffner; Jean Rice; Dr. Cynthia T. French; on behalf of the Editorial Leadership Team.

Point Counterpoint Editorial

POINT: Will New Anti-eosinophilic Drugs Be Useful In Asthma Management?
Yes. Dr. P.M. O'Byrne
No. Dr. P. Barnes

Giants in Chest Medicine

Dr. Claude Lenfant. By Dr. E.J. Roccella.

Special Feature

The Eighth Edition Lung Cancer Stage Classification. By Dr. F.C. Detterbeck, et al.

Evidence-based Medicine

Liberation From Mechanical Ventilation in Critically Ill Adults: Executive Summary of an Official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline. By Dr. G.A. Schmidt, et al.

Original Research

Effect of Procalcitonin Testing on Health-care Utilization and Costs in Critically Ill Patients in the United States. By Dr. R.A. Balk, et al.

Use of Palliative Care in Patients With End-Stage COPD and Receiving Home Oxygen: National Trends and Barriers to Care in the United States. By Dr. B. Rush, et al.

SLEEP STRATEGIES: Sleep-disordered breathing and pregnancy complications: Emerging data and future directions

BY FRANCESCA FACCO, MD

Background

Sleep-disordered breathing (SDB) conditions are characterized by abnormal respiratory patterns and abnormal gas exchange during sleep.[1-3] Obstructive sleep apnea (OSA), the most common type of SDB, is characterized by repetitive episodes of airway narrowing during sleep that lead to respiratory disruption, hypoxia, and sleep fragmentation. In reproductive-aged women, epidemiologic studies suggest a 2% to 13% prevalence of OSA.[4-6] Pregnancy is associated with changes that promote OSA, such as weight gain and edema of the upper airway.[7] Frequent snoring, a common symptom of OSA, is endorsed by 15% to 25% of pregnant women.[8-10] Health outcomes that have been linked to SDB in the nonpregnant population, such as hypertension and insulin-resistant diabetes, have clinically relevant correlates in pregnancy (preeclampsia, gestational diabetes).[11-13] The underlying mechanistic pathways linking SDB and adverse pregnancy outcomes are likely multifactorial. SDB leads to oxidative stress, autonomic dysfunction, inflammation, endothelial damage, and altered hormonal regulation of energy expenditure.[14] These same biologic pathways have been linked to adverse pregnancy outcomes.[15]

DR. FACCO

While several retrospective and cross-sectional studies suggest that SDB may increase the risk of developing hypertensive disorders and gestational diabetes during pregnancy,[16-18] up until recently, there were limited and conflicting data from prospective observational cohorts in which SDB exposure and pregnancy outcomes have been methodically measured and confounding variables carefully considered.[19-21] Louis et al.[19] reported on a cohort of 175 obese women and demonstrated that women with SDB (apnea-hypopnea index greater than or equal to 5) were more likely to develop preeclampsia (adjusted odds ratio, 3.5; 95% CI, 1.3, 9.9). However, two other small studies failed to demonstrate a positive association between SDB and pregnancy-related hypertension, but one suggested a relationship between SDB and gestational diabetes.[20,21]

Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be Sleep-Disordered Breathing Substudy

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be Sleep-Disordered Breathing Substudy (nuMoM2b-SDB) was a prospective cohort study.[22,23] Level 3 home sleep tests were performed using a six-channel monitor that was self-applied by the participant twice during pregnancy, first between 60 and 150 weeks of pregnancy and then again between 220 and 310 weeks. An apnea-hypopnea index (AHI) of at least 5 was used to define SDB. The study was powered to test the primary hypothesis that SDB occurring in pregnancy is associated with an increased incidence of preeclampsia. Secondary outcomes were rates of hypertensive disorders of pregnancy, defined as preeclampsia and prenatal gestational hypertension, and gestational diabetes. Crude and adjusted odds ratios and 95% confidence intervals were calculated from univariate and multivariate logistic regression models. Adjustment covariates included maternal age (less than or equal to 21, 22-35, and over 35 years), body mass index (less than 25, 25 to less than 30, greater than or equal to 30 kg/m^2), chronic hypertension (yes, no), and, for midpregnancy, rate of weight gain per week between early and midpregnancy assessments, treated as a continuous variable.

There were 3,705 women enrolled. AHI data were available for 3,132 (84.5%) and 2,474 (66.8%) women in early and midpregnancy, respectively. The corresponding prevalence of SDB was 3.6% and 8.3%. The overall prevalence of preeclampsia was 6.0%; hypertensive disorders of pregnancy, 13.1%; and gestational diabetes, 4.1%. In early and midpregnancy, the adjusted odds ratios for preeclampsia when SDB was present were 1.94 (95% CI, 1.07-3.51) and 1.95 (95% CI, 1.18-3.23), respectively; hypertensive disorders of pregnancy, 1.46 (95% CI, 0.91-2.32) and 1.73 (95% CI, 1.19-2.52); and gestational diabetes mellitus, 3.47 (95%, CI 1.95-6.19) and 2.79 (95% CI, 1.63-4.77). Additionally, increasing exposure-response relationships were observed between AHI and both hypertensive disorders and gestational diabetes.[23]

	Early Pregnancy (6-15 weeks)		Midpregnancy (22-31 weeks)	
	AHI < 5	AHI ≥ 5	AHI < 5	AHI ≥ 5
Preeclampsia	170/3017 (5.6)	16/114 (14.0)	114/2266 (5.0)	26/206 (12.6)
Hypertensive disorders of pregnancy	378/3017 (12.5)	28/114 (24.6)	266/2266 (11.7)	51/206 (24.8)
Gestational diabetes	107/2965 (3.6)	21/110 (19.1)	69/2231 (3.1)	27/201 (13.4)

Conclusions and future directions

The nuMoM2b data are provocative because sleep apnea is a potentially modifiable risk factor for adverse pregnancy outcomes. While a majority of SDB cases identified during pregnancy were mild, the nuMoM2b data demonstrate that even modest elevations of AHI in pregnancy are associated with an increased risk of developing hypertensive disorders and an increased incidence of gestational diabetes.

Pregnancy is conceivably an ideal scenario in which to better understand the role of SDB treatment as a preventive strategy for reducing cardiometabolic morbidity as the time frame needed to measure incident outcomes after initiating therapy is significantly contracted. However, data regarding the role of OSA treatment with continuous positive airway pressure (CPAP) during pregnancy, both regarding its acceptability to patients and its therapeutic benefit, are extremely limited. Further research is needed to establish whether universal screening for and treating of SDB in pregnancy can mitigate the risks and consequences of hypertensive disorders of pregnancy and gestational diabetes. However, in the meantime, we have to recognize that as our obstetric patient population is becoming more obese, we will encounter more women with symptomatic SDB in pregnancy. It is well documented that patients with symptomatic SDB, those who report that their snoring leads to chronic sleep disruption and excessive daytime sleepiness, can benefit from CPAP in terms of sleep quality and daytime function. Therefore, in addition to encouraging women already prescribed CPAP to continue their therapy during pregnancy, obstetricians who encounter a patient reporting severe SDB symptoms should refer her to a sleep specialist for further evaluation.

Dr. Facco is assistant professor, department of obstetrics and gynecology, University of Pittsburgh, Magee-Women's Hospital, Magee Women's Research Institute.

References

1. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med.* 2012;8(5):597-619.
2. Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clin Proc.* 2011;86(6):549-54; quiz, 554-5.
3. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* 1st ed. Westchester, Ill.: American Academy of Sleep Medicine, 2007.
4. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013 May 1;177(9):1006-14.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328(17):1230-5.
6. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med.* 2003;167(9):1181-5.
7. Pien GW, Schwab RJ. Sleep disorders during pregnancy. *Sleep.* 2004;27(7):1405-17.
8. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mothers' sleep. *Sleep Med.* 2002;3(1):37-42.
9. Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep.* 2005;28(10):1299-1305.
10. Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. *Obstet Gynecol.* 2010;115(1):77-83.
11. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* 2000;342(19):1378-84.
12. Punjabi NM, Shahar E, Redline S, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *Am J Epidemiol.* 2004;160(6):521-30.
13. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: A population-based study. *Am J Respir Crit Care Med.* 2005;172(12):1590-5.
14. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010;90(1):47-112.
15. Romero R, Badr MS. A role for sleep disorders in pregnancy complications: Challenges and opportunities. *Am J Obstet Gynecol.* 2014;210(1):3-11.
16. O'Brien LM, Bullough AS, Owusu JT, et al. Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: Prospective cohort study. *Am J Obstet Gynecol.* 2012;207(6):487.e1-9
17. Chen YH, Kang JH, Lin CC, Wang IT, Keller JJ, Lin HC. Obstructive sleep apnea and the risk of adverse pregnancy outcomes. *Am J Obstet Gynecol.* 2012;206(2):136.e1-5.
18. Bourjeily G, Raker CA, Chalhoub M, Miller MA, et al. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. *Eur Respir J.* 2010;36(4):849-55.
19. Louis J, Auckley D, Miladinovic B, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. *Obstet Gynecol.* 2012;120:1085-92.
20. Facco FL, Ouyang DW, Zee PC, et al. Implications of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol.* 2014 Jun;210(6):559.e1-6.
21. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. *Thorax.* 2014;69(4):371-7.
22. Facco FL, Parker CB, Reddy UM, et al. NuMoM2b Sleep-Disordered Breathing study: Objectives and methods. *Am J Obstet Gynecol.* 2015 April;212(4):542.e1–542.e127.
23. Facco FL, Parker CB, Reddy UM, et al. Association between sleep-disordered breathing and hypertensive disorders of pregnancy and gestational diabetes mellitus. *Obstet Gynecol. ePub.* 2016 Dec 2.

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

gsk | Theravance

For appropriate adult patients

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$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

BOXED WARNING CONTINUED ON NEXT PAGE

Please see additional Important Safety Information for BREO on pages 2–4.
Please see accompanying Brief Summary of Prescribing Information, including Boxed Warning, for BREO on pages 5–7.

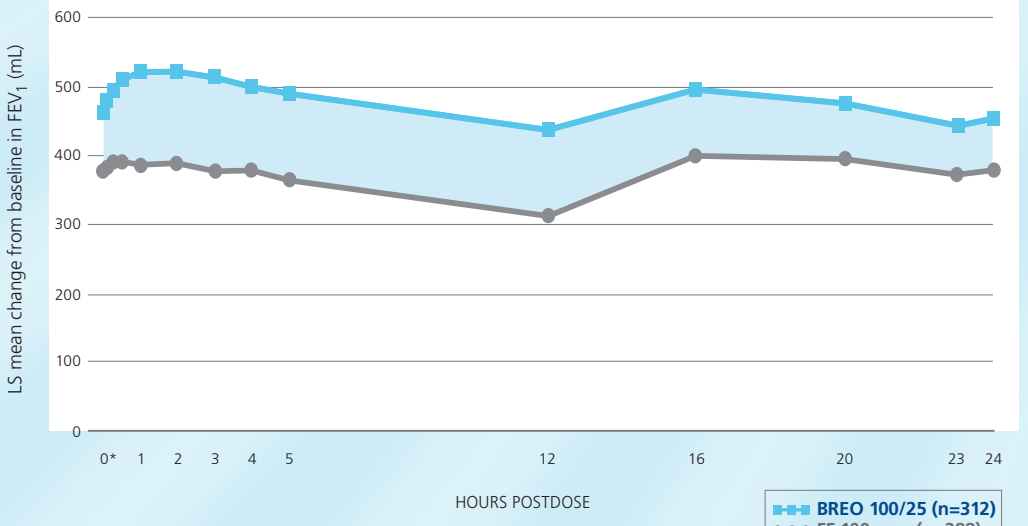
BREO:
CONTINUOUS LUNG FUNCTION IMPROVEMENT

In patients with **asthma** uncontrolled on an ICS

BREO 100/25 (n=312) provided a 108-mL improvement from baseline in weighted mean (wm) FEV_1 (0-24 hours) vs fluticasone furoate (FF) 100 mcg (n=288) at Week 12 (*P*<0.001).[1]

BREO 100/25

SERIAL FEV_1 (0-24 HOURS) AT WEEK 12[1]



*Zero=dose administered in the evening.

Study description

Design: 12-week, randomized, double-blind study that evaluated the safety and efficacy of BREO 100/25, BREO 200/25, and FF 100 mcg (each administered once daily in the evening). Patients who reported symptoms and/or rescue $beta_2$-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 FEV_1 of 62%.

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

Primary endpoint: wm FEV_1 (0-24 hours) at Week 12.

Weighted mean FEV_1 (0-24 hours) was calculated from predose FEV_1 (within 30 minutes of dose) and postdose FEV_1 after 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours.

FEV_1=forced expiratory volume in 1 second; LS=least squares.

In a placebo-controlled 12-week study[2]:

- **wm FEV_1:** in a subset of patients, BREO 100/25 (n=108) demonstrated a numerically greater improvement in change from baseline in wm FEV_1 (0-24 hours) compared with FF 100 mcg (n=106) of 116 mL (95% CI: –5, 236; *P*=0.06) and a statistically significant 302-mL improvement (*P*<0.001) compared with placebo (n=95) at Week 12.

Study description: 12-week, randomized, double-blind, placebo-controlled study of 609 patients aged 12 years and older[†] (mean age: 40 years) with asthma, symptomatic on low- to mid-dose ICS (FP 100 mcg to 250 mcg twice daily or equivalent) during a 4-week run-in period (mean baseline percent predicted FEV_1 of 70%) randomized to BREO 100/25, FF 100 mcg, or placebo (each administered once daily in the evening). The co-primary endpoints were weighted mean FEV_1 (0-24 hours) (in a subset of patients) and trough FEV_1 at Week 12.

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

Important Safety Information (cont'd)

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

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

CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

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

WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

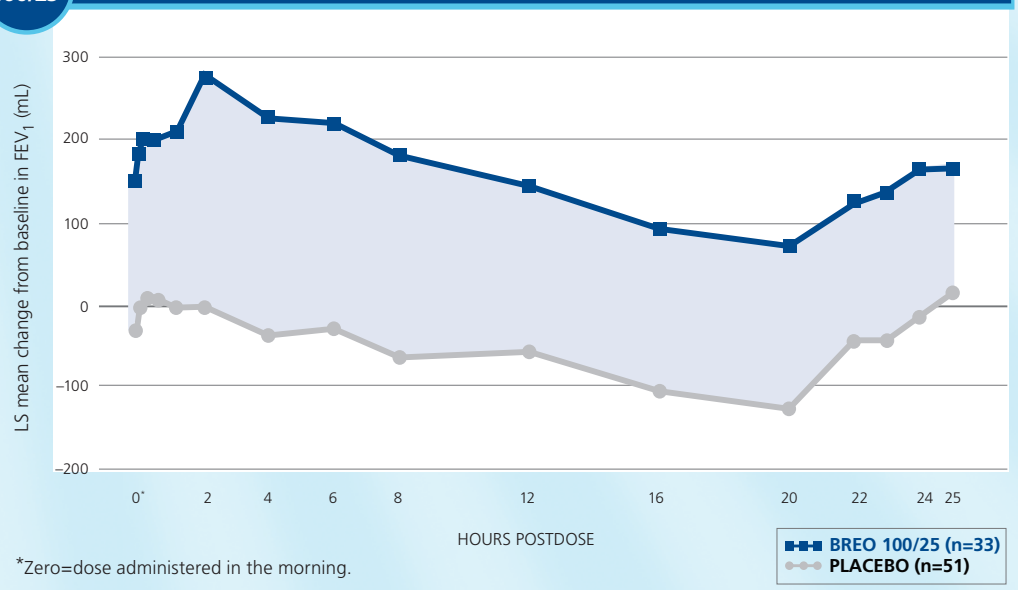
FOR A FULL 24 HOURS, WITH JUST ONE DAILY INHALATION

In patients with COPD

BREO 100/25 (n=33) provided a 220-mL improvement from baseline in wm FEV_1 (0-24 hours) vs placebo (n=51) at end of the 28-day treatment period (*P*<0.001).[3,4]

BREO 100/25

SERIAL FEV_1 (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29[3,4]



*Zero=dose administered in the morning.

Study description

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

Patients: 54 patients (mean age: 58 years) with COPD who had a mean percent predicted postbronchodilator FEV_1 of 50% and a mean postbronchodilator FEV_1/FVC ratio of 53%.

Primary endpoint: wm FEV_1 (0-24 hours) at end of 28-day treatment period.

Secondary endpoint: serial FEV_1 (0-25 hours) assessed over 1 full day at Days 28 and 29.

FVC=forced vital capacity.

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

In a separate 6-month lung-function study: a randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs FF 100 mcg and vs placebo (each administered once daily) on lung function in 1030 patients (mean age: 63 years) with COPD.[§] For the co-primary endpoints, BREO significantly improved wm FEV_1 (0-4 hours) postdose on Day 168 by 120 mL vs FF[‖] and 173 mL vs placebo (*P*<0.001 for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV_1 at Day 169 of 115 mL vs placebo (95% CI: 60, 169; *P*<0.001); the 48-mL difference vs vilanterol (VI) 25 mcg[¶] did not achieve statistical significance (95% CI: –6, 102; *P*=0.082).[3,5]

[§]At screening, patients had a mean postbronchodilator percent predicted FEV_1 of 48% and a mean postbronchodilator FEV_1/FVC ratio of 48%.
[‖]The wm comparison of BREO with FF, the ICS component, evaluated the contribution of VI to BREO. ICS are not approved as monotherapy for COPD.
[¶]The trough FEV_1 comparison of BREO with VI, the LABA component, evaluated the contribution of FF to BREO. VI is not approved as monotherapy.

Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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

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

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

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

BREO® ELLIPTA®
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CONSIDER **24-HOUR BREO** TODAY

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

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

ADVERSE REACTIONS: BREO 100/25 FOR COPD

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

ADVERSE REACTIONS: BREO FOR ASTHMA

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Please see additional Important Safety Information for BREO on pages 1–3.

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

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BREO® ELLIPTA®
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BRIEF SUMMARY

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

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

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

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

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

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease:
BREO 100/25 is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 once daily is the only strength indicated for the treatment of COPD.
Important Limitation of Use: BREO is NOT indicated for the relief of acute bronchospasm.

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO 100/25 no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO 100/25 is not appropriate in this situation.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO.

BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Excessive Use of BREO and Use with Other Long-Acting Beta$_2$-Agonists:
BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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

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

In replicate 12-month trials in 3,255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg: 6% (48 of 820 subjects); BREO 100/25: 6% (51 of 806 subjects); or BREO 200/25: 7% (55 of 811 subjects) than in subjects receiving vilanterol 25 mcg: 3% (27 of 818 subjects). There was no fatal pneumonia in subjects receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (less than 1% for each treatment group).

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

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

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

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

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

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

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

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:
Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,

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

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

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

5.12 Cardiovascular Effects:
Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

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

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

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

5.15 Coexisting Conditions:
BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

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

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

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]* Systemic and local corticosteroid use may result in the following: *Candida albicans* infection *[see Warnings and Precautions (5.4)]*; Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*; Immunosuppression *[see Warnings and Precautions (5.6)]*; Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*; Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

6-Month Trials: The incidence of adverse reactions associated with BREO 100/25 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n=1,224 and n=1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were white. They had a mean age of 62 years and an average smoking history of 44 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%). Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

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

12-Month Trials: Long-term safety data is based on two 12-month trials (Trials 3 and 4; n=1,633 and n=1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were white. They had a mean age of 64 years and an average smoking history of 46 pack-years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO 100/25, BREO 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions previously mentioned, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO 100/25 (n=806) for 12 months included back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

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

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

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

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

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

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

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

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

6.3 Postmarketing Experience:
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of BREO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO or a combination of these factors.
Cardiac Disorders: Palpitations, tachycardia.
Immune System Disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.
Musculoskeletal and Connective Tissue Disorders: Muscle spasms.
Nervous System Disorders: Tremor.
Psychiatric Disorders: Nervousness.
Respiratory, Thoracic, and Mediastinal Disorders: Paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4:
Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants:
Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

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

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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 $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because animal reproduction studies are not always predictive of human response, BREO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO.

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

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

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

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

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

8.3 Nursing Mothers:
It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO by nursing mothers, caution should be exercised when it is administered to a nursing woman.

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

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

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

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

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

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

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

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

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

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

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

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

Not for Acute Symptoms:
Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-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 $beta_2$-agonists; need for more inhalations than usual of inhaled, short-acting $beta_2$-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 $Beta_2$-agonists:
Instruct patients not to use other LABA for COPD and asthma.

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

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

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

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

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

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

Risks Associated with Beta-agonist Therapy:
Inform patients of adverse effects associated with $beta_2$-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.

GlaxoSmithKline
Research Triangle Park, NC 27709

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The CHEST Foundation thanks you for your generous support in 2016!

You are our champions for lung health.

Lung Health Experience

Charity Sunshine Tillemann-Dick performing at the CHEST Foundation Awards Ceremony.

20th Anniversary Reception

Breakfast of Champions

Young Professionals Reception

Winners-All at CHEST 2016

We all know that, with the great success of CHEST 2016, everyone who shared that event is a winner. But, we would especially like to call out some of the special winners who were recognized during our annual meeting.

CHEST Awards

College Medalist Award
Lewis J. Rubin, MD, FCCP

Distinguished Service Award
Kim D. French, MHSA, CAPPM, FCCP

Alfred Soffer Award for Editorial Excellence
Seth J. Koenig, MD, FCCP

Master Clinician Educator Award
Jack D. Buckley, MD, MPH, FCCP

Distinguished Scientist Honor Lecture
Jay Nadel, MD

Edward C. Rosenow III, MD, Master FCCP/ Master Teacher Honor Lecture
Suhail Raoof, MBBS, FCCP

Murray Kornfeld Memorial Founders Lecture
Michael Niederman, MD, FCCP
Pasquale Ciaglia Memorial Lecture
Kevin L. Kovitz, MD, FCCP

Roger C. Bone Memorial Lecture
Robert A. Berg, MD
Thomas L. Petty, MD, Master FCCP Memorial Lecture
Nicola A. Hanania, MD, MS, FCCP

Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation
Thomas G. Keens, MD
Om P. Sharma, MD, Master FCCP Memorial Lecture
Robert P. Baughman, MD, FCCP

Early Career Educator
Gabriel Bosslet, MD, FCCP

CHEST Challenge Championship 2016

1st Place
The University of Arizona
Huthayfa Ateeli, MBBS
Naser Mahmoud, MD
Muna Omar, MD, MBBS
PD: James L. Knepler Jr.

2nd Place
New York Methodist Hospital
Anu R. Jacob, MD
Stephen D. Milan, MD
Jordan Taillon, MD
PD: Anthony G. Saleh, MD, FCCP

3rd Place
Interfaith Medical Center
Chidozie C. Agu, MD
Saroj P. Kandel, MBBS
Divya Salhan, MD, MBBS
PD: Marie Frances J. Schmidt, MD, FCCP

CHEST Foundation Grant Winners

GlaxoSmithKline Distinguished Scholar in Respiratory Health
Don Hayes Jr., MD, FCCP
The Research Institute at Nationwide Children's Hospital
Implications of the Lung Allocation Score in Prioritizing Critically Ill Patients for Lung Transplantation
Supported by GlaxoSmithKline.

2016 Research Grantees

Alice Turner, MBChB, MRCP, PhD
University of Birmingham, United Kingdom
CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
Improving Access to Augmentation: A Propensity-Matching Study Between the UK AATD Registry and AlphaNet
This grant is jointly supported by the CHEST Foundation and the Alpha-1 Foundation.

Robert Busch, MD
Brigham and Women's Hospital, Channing Division of Network Medicine
CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
Methylation Quantitative Trait Loci: Markers of Race-Specific Disparities in African Americans With COPD
This grant is supported by AstraZeneca.

Clemens Grassberger, PhD
Massachusetts General Hospital – Harvard University
CHEST Foundation Research Grant in Lung Cancer
Dynamic FLT-PET as Biomarker for Early Response in Locally Advanced Lung Cancer Patients
This grant is supported by Genentech Inc.

Cristina Russo, MD, PhD
Bambino Gesù Children's Hospital, Rome, Italy
CHEST Foundation Research Grant in Nontuberculous Mycobacteria
A Proteomic-Metaproteomic Analysis Approach Allows Identification of Drug Target Candidates for the Future Design of Preventive, Diagnostic, and Therapeutic Strategies Against Nontuberculous Mycobacteria Diseases
This grant is supported by Insmed.

Peter Leary, MD, MS
University of Washington
CHEST Foundation Research Grant in Pulmonary Arterial Hypertension
Expression Profiling in Pulmonary Arterial Hypertension
This grant is supported by Actelion Pharmaceuticals, US, Inc.

Brett Ley, MD
University of California, San Francisco
CHEST Foundation Research Grant in Pulmonary Fibrosis
Extracellular Circulation RNAs as Predictors of Disease Progression in Idiopathic Pulmonary Fibrosis
This grant is supported by Boehringer Ingelheim Pharmaceuticals & Genentech Inc.

Sydney Montesi, MD
Massachusetts General Hospital
CHEST Foundation Research Grant in Pulmonary Fibrosis
Gadofosveset-Enhanced Lung MRI to Detect Idiopathic Pulmonary Fibrosis Disease Activity
This grant is supported by Boehringer Ingelheim Pharmaceuticals & Genentech Inc.

Farbod Rahaghi, MD, PhD
Brigham and Women's Hospital
CHEST Foundation Research Grant in Venous Thromboembolism
CT Scan-Based Markers for Prediction of Outcomes in Acute Pulmonary Embolism
This grant is supported by Daiichi Sankyo.

Catherine Oberg, MD
Icahn School of Medicine at Mount Sinai
CHEST Foundation Research Grant in Women's Lung Health
Effects of Household Air Pollution on Airway Inflammation, Lung Function, and Respiratory Symptoms
This grant is supported in full by the CHEST Foundation.

2016 Community Service Grantee

Ethel Jane Carter, MD, FCCP
Warren Alpert School of Medicine at Brown University
CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP
East African Training Initiative (EATI) in Pulmonary Medicine

2016 NetWorks Challenge Travel Grantees

Debarsee Banerjee, MS, MD
Women's Health NetWork

Drew Harris, MD
Occupational and Environmental Health NetWork

Kerry Hena, MD
Occupational and Environmental Health NetWork

Amanpreet Kaur, MD
Women's Health NetWork

2016 Diversity Travel Grant Winners

John B. Bishara, DO
Renato F. Blanco Jr., MD
Angel Coz-Yataco, MD
Sherie A. Gause, MD
Anthony Nebor, MD
James T. Williams, MD

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Alfred Soffer Research Award Winners

Kerry Hena, MD

Deepak Pradhan, MD, FCCP

Young Investigator Award Winners

Elizabeth Becker: Clinical Characteristics of Sarcoidosis in World Trade Center (WTC) Exposed Fire Department of the City of New York (FDNY) Firefighters

Daniel Altman, MD: Cost-Effectiveness of Universally Funding Smoking Cessation Pharmacotherapy

Top 3 Poster Winners

Epaminondas Kosmas, MD, PhD, FCCP: Bronchiectasis in Patients With COPD: An Irrelevant Imaging Finding or a Clinically Important Phenotype?

Mark Regala, MD, BS: Evaluation of Outcomes of Post-Extubation Dysphagia in Elderly Patients

Massa Zantah, MD: Correlation of Esophageal Dilatation and Pulmonary Fibrosis in Scleroderma

Runner-up: Alev Gurgun, MD: Pulmonary Rehabilitation Response in Elderly and Younger Patients With COPD

Case Report Slide Winners

John Egan, MD, BA: An Unusual Cause of Tracheal Stenosis Due to a Vascular Anomaly Successfully Managed With Silicone Airway Stenting Prior to Definitive Vascular Repair

Harprett Grewal, MD: Bladder PTLD: First Reported Case of Post-Transplant Lymphoproliferative Disorder (PTLD) in the Bladder in a Lung Transplant Recipient

Michael Fingerhood, MD, MPH: Pulmonary Overlap Histiocytosis: A Rare Case of Interstitial Lung Disease Due to Erdheim Chester Disease in a Patient With Langerhans Cell Histiocytosis and Myelodisplastic Syndrome

Yihenew Negatu, MD: Acute ST Elevation Myocardial Infarction Related to Carbon Monoxide Poisoning in a Young Patient Without Coronary Artery Disease

Stephanie Wappel, MD: False-Negative Pet Imaging in Early Stage Malignant Pleural Mesothelioma

Lina Miyakawa, MD: Restrictive EGFR Mutation

Jeffrey Bonenfant, DO: A Unique Case of Follicular Bronchiolitis

Melissa Myers, MD: Seeing the Forest and Not Just the Trees: A Case of Recurrent Fever, Cough, and Respiratory Failure

Carly Fabrizio, DO: An Unusual Case of Submassive Hemoptysis

Meilinh Thi, DO: A Case to Make Your Skin Crawl

Garrett Harp, MD: Lambertosis: A Lung Cancer Mimic

Malik Khan, MD: Pleural Epithelioid Hemangioendothelioma: A Case Report

Priya Patel, MD: A Troubling Trifecta: Pulmonary Alveolar Proteinosis and Pneumocystis Pneumonia in Acute Myeloid Leukemia

Atul Palkar, MD: SGLT2 Inhibitors: Mind the Gap

Ji Yeon Lee, MD: Making Unusual Connections: Fibrosing Mediastinitis Leading to Bronchoesophageal Fistula

Sailm Daouk, MD: A Rare Form of Invasive Aspergillus Infection in a Severely Immunocompromised Host

Venkata Ravi Kumar Angirekula, MD: Vanishing Lung

Stephen Milan, MD: An Unexpected Mass

Lelia Logue, MD: A Rare Cause of Dysphagia

Daniel Hershberger, MD: Rapidly Progressive Hypoxic Respiratory Failure After a Rash: A Case of Clinically Amyopathic Dermatomyositis (CADM)-Associated ILD

Fellow Case Report Poster Winners

Krishna Siva Sai Kakkera
An Unusual Case of Crypotococcal Pleural Effusion

George Cheng
Use of Laparoscopic Suction Irrigator With Rigid Pleuroscope in Medical Thoracoscopy

Matt Koroscil
Wong Type Dermatomyositis Complicated by Interstitial Lung Disease

Derek Hansen
Acute Fibrinous and Organizing Pneumonia Following Hematopoietic Stem Cell Transplantation Responsive to Corticosteroid Therapy

Ala Eddin Sagar
Pulmonary Embolism Caused by Thrombin-Based Hemostatic Matrix After Discectomy

Sandeep Chennadi
Systemic Lupus Erythematosus (SLE) With Refractory Bilateral Chylothorax and Chylous Ascites

Medical Student/Resident Case Report Poster Winners

Justin Fiala
Pulmonary Presentation Without Concurrent Bone Involvement in Erdheim-Chester Disease: A Report of Two Cases

Navitha Ramesh
A Fatal Migration: A Case of Intra-Cardiac Embolization of a Peripheral Stent

Humna Abid Memon
Use of Extracorporeal Membrane Oxygenation in Postpartum Management of a Patient With PAH

Vanessa Ohleyer
A Case of Unusual Anatomy for an Uncommon Mediastinal Tumor

Tanushree Gahlot
Three Unusual Presentations of Job's Syndrome (Hyper Immunoglobulin E Syndrome)

NetWorks Challenge Winners

Round 1
Women's Lung Health NetWork
Round 2
Practice and Operations NetWork-1st place
Home-Based Mechanical Ventilation and Neuromuscular Disease NetWorks – 2nd place
Round 3
Home-Based Mechanical Ventilation, Neuromuscular Disease, and the Women's Lung Health NetWorks

CHEST Bingo Winners

Youseff Anid, MD, FCCP
Karen Cochran, ACNP
Molly Howsware, DO
Katie Jeans, MD
Genovena Medina, RN
Gregory Eisinger, MD
Saurabh Mittal, MD, MBBS
Navitha Ramesh, MD
Dalvinder Dhillon, MD
Teresita Saylor, MD, FCCP
Carl Kaplan, MD, FCCP
Vishal Patel, MBBS, FCCP
Erin Peterson, CNP
Lilian Pereira, DO

Four women have served as CHEST Presidents, and three of them were able to catch up at CHEST in Los Angeles. From the left are Susan Pingleton, MD, Master FCCP; Barbara Phillips, MD, MSPH, FCCP; and Kalpalatha Guntupalli, MD, Master FCCP. Deborah Shure, MD, Master FCCP, our first woman President, is not pictured.

The CHEST Council of Global Governors met at CHEST in Los Angeles.

NETWORKS: Pneumonia Day, evaluating inhalers, tobacco taxes

Chest Infections

Pneumonia Day: Today is the day to act!

This past November 12, we celebrated "Pneumonia Day," named for a disease that has little connotation in the real world, because of the perception that we need only a short course of antibiotics to get better. Such is the origin of the term "walking pneumonia," which emphasizes that we can still walk even while sick with pneumonia.


DR. RESTREPO

However, we recently experienced the most important moment of awareness related to this condition, when one of the U.S. presidential candidates became sick with that disease known as "pneumonia."

Suddenly, the media devoted great interest to explore this condition, as if it were a new outbreak or a rare disease that could potentially kill someone. Even the health-care providers seem to believe that "pneumonia" is not a big deal, ignoring the fact that it is the most common infectious cause of death overall, and that it not only affects children but also the elderly and patients with poor immune systems.

One out of nine patients who are admitted to the hospital for pneumonia may die during the hospitalization, and one out of four patients who get admitted to an ICU may not survive the event.

However, it also highlights that pneumonia is more than just an acute disease, compromising the brain, heart, and kidneys. In the long run, even after surviving the hospitalization for pneumonia, it can kill and cause other well-known complications leading to death, such as myocardial infarction, arrhythmias, heart failure, and sudden cardiac death.

Please, stop for one moment and ask yourself about your role in preventing pneumonia and pneumonia-related deaths in your communities. The Chest Infections NetWork is here to help you advocate for the common goal of solving this problem.

Marcos I. Restrepo, MD, MSc, FCCP
Steering Committee Member

Clinical Pulmonary Medicine

Delivery makes a difference: Providing inhaled medication to your patients

One might ask why CHEST (American College of Chest Physicians) and Sunovion developed a steering committee of experts in the field of obstructive lung disease to evaluate the knowledge, attitudes, beliefs, and practices of physicians and other health-care professionals related to inhalational medicines and devices. While inhalers are approved by the FDA Center for Drug Evaluation Research (CEDER) as drug and device

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combination, the process assesses reproducibility and shelf-life but does not address the real-world situation that each of us face with individual patients. How often do clinicians consider the characteristics of each delivery system, as well as the medication being delivered? One might be surprised at the answer.

Patients are frequently prescribed several types of devices with different instructions for optimal use. For example, dry powder inhalers often require high flow rates (30-90 L/min) to deaggregate powder pellets into particles less than 5 mcm, while metered-dose inhalers require a slow inspiratory flow (less than 30 L/min). Patients who use both types of devices often confuse which inspiratory flow rate to use with which devices, despite proper education and training. This does not even take into consideration the variable number of steps required by various inhalational devices (which can be as few as 3 steps to as many as 12 steps). Additionally, studies demonstrate that peak inspiratory flow rates, inspiratory volumes, and drug deposition in the lungs may be

DR. PETERS

influenced by gender, height, and weight; as well as by the degree of pulmonary reserve and hyperinflation.

Are there data to suggest that these questions impact the care of patients with severe asthma or COPD? I eagerly await the results of the survey.

Jay I. Peters, MD, FCCP
Steering Committee Member

Interprofessional Team

A California victory for tobacco control

Californians approved Proposition 56, "Cigarette Tax to Fund Healthcare, Tobacco Use Prevention, Research, and Law Enforcement." This measure increases the excise tax on all forms of tobacco by $2.00. For the first time, it applies to electronic products that vaporize nicotine that were previously only subject to sales tax. This is in addition to federal excise taxes ($1.01) and state and local sales taxes ($0.50 to $0.60). (https://ballotpedia.org/California_Proposition_56,_Tobacco _Tax_Increase_(2016)

When Prop 56 goes into effect April 1, 2017, the average price of a package of cig-

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DR. ROTH

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arettes will increase to at least $7.89. Based on data from the Surgeon General's report on "Preventing Tobacco Use Among Youth and Young Adults," this tax increase should equate with a fall in smoking rates by about 12%. Youth and young adults are particularly susceptible to price increases, which helps prevent smoking initiation or continuation.

Tobacco-related health-care costs Californians $3.5 billion dollars annually (Official Voter Information Guide, 2016). Funds raised by Prop 56 will be used by state and local health programs such as Medi-Cal to defray the costs of smoking prevention programs, smoking cessation, and treatment of tobacco-related illnesses (California Tobacco Control Program).

Prop 56 expands on tougher laws implemented in 2016 that expanded the workplace prohibition of smoking, increased fees for tobacco retailers and wholesalers, broadened the definition of smoking to include e-cigarettes, and increased the minimum age to purchase tobacco to 21 years old. Combined, these measures are expected to result in a further decline in tobacco usage in California.

Alan Roth, RRT, MS, FCCP
Steering Committee Member

Bronchoscopy sedation changes in 2017

BY MICHAEL NELSON, MD, FCCP

A major change in coding for bronchoscopy occurred on January 1, 2017, as moderate (conscious) sedation is now separately identified from the work relative value units (wRVUs) for the bronchoscopy codes. While traditionally the bronchoscopist provided moderate sedation, in recent clinical practice, other individuals often provide the sedation. CMS mandated refinement of separate Current Procedural Terminology (CPT®) codes to account for the work of moderate procedural sedation. In the final rule published in November 2016, CMS removed 0.25 wRVUs from many of the bronchoscopy codes to account for the work of moderate sedation. To be reimbursed appropriately, include a moderate sedation CPT code with all bronchoscopy procedures.

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Total intraservice time	Patient age	Moderate sedation performed by *Bronchoscopist* Codes	*Second provider* Codes
Less than 10 minutes	Any age	Not reported separately	
15-22 minutes	< 5 years	**99151**	**99155**
	>5 years	**99152**	**99156**
23-37 minutes	< 5 years	**99151 + 99153**	**99155 + 99157**
	>5 years	**99152 + 99153**	**99156 + 99157**
38-52 minutes	< 5 years	**99151 + 99153** x2	**99155 + 99157** x2
	>5 years	**99152 + 99153** x2	**99156 + 99157** x2

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Use codes **99151** and **99155** for patients younger than 5 years. For a patient 5 years or older, when the bronchoscopist provides moderate sedation, report code **99152** for the initial 15 minutes and **99153** for subsequent time in 15-minute increments. For a patient 5 years or older, when a provider other than the bronchoscopist provides moderate sedation, use code **99156** for the initial 15 minutes and **99157** for subsequent time in 15-minute increments. Utilize codes **99156** and **99157** only when a second provider (other than the bronchoscopist) performs moderate sedation in the facility setting (eg, hospital, outpatient hospital/ambulatory surgery center, skilled nursing facility). When the second provider performs these services in the nonfacility setting (eg, physician office, freestanding imaging center), do not report codes **99155**, **99156**, or **99157**. Moderate sedation does not include minimal sedation (anxiolysis), deep sedation, or monitored anesthesia care (**00100-01999**).

Do not use a moderate sedation code (**99151-2** or **99155-6**) if providing less than 10 minutes of moderate sedation. As with other time-based codes, use the subsequent codes **99153** and **99157** when moderate sedation lasts 8 minutes or longer than the initial 15 minutes. The time for moderate sedation begins with the administration of the sedating agent and concludes when the continuous face-to-face presence of the bronchoscopist ends after completion of the procedure. Intermittent, re-evaluation of the patient afterward is postservice work and is not included in the time for moderate sedation. For example, if the bronchoscopist provides moderate sedation for 25 minutes in a 65-year-old man, report **99152** (for the initial 15 minutes) and **99153** (for the subsequent 10 minutes). If an individual other than the bronchoscopist provides moderate sedation for 41 minutes in a 57-year-old woman, use **99156** (for the initial 15 minutes) and two units of **99157** (for the subsequent 26 minutes). If a bronchoscopist provides moderate sedation and reports the appropriate codes after January 1, the 0.25 wRVU change will have no financial impact compared with 2016. If a second provider performs the moderate sedation, expect an approximately $8.72 drop in reimbursement per procedure.

IMPORTANT REMINDER

Claiming CHEST 2016 CME/MOC

The deadline for claiming CME/MOC for CHEST 2016 is February 28, 2017. Additionally, due to a deadline imposed by ABIM, all MOC from all 2016 activities must be claimed by February 28, 2017. After this date, ABIM will no longer accept MOC from 2016 activities. Please note: depending on your recertification cycle, you may need points prior to the 2017 deadline. Please refer to your ABIM diplomate's record and/or contact ABIM for questions specific to your individual board certification.

Joint CHEST-SGP Congress 2017

Join leaders in CHEST medicine for a program designed by clinicians for clinicians.

ANDERM/THINKSTOCK

Basel, Switzerland June 7-9
Join leaders in CHEST medicine for a program designed by clinicians for clinicians.

The Joint Congress organized by CHEST and the Swiss Society of Pneumology will be held from June 7-9 in Basel, Switzerland. The program has been designed by more than 140 faculty members from both the United States and Europe, and it aims to provide a robust overview of all aspects of respiratory medicine through interactive sessions, plenary discussions, critical appraisals on controversial topics, and a review of the last year of published works.

The Joint Congress also provides the opportunity to take part in hands-on simulation in areas such as lung function techniques including body plethysmography, N2 washout techniques, and respiratory physiotherapy. Another hands-on opportunity is the interventional pneumology CHEST experience course, which will be held from 8:00 AM-11:00 AM on June 7 and 8 on site. This course will provide an overview of conventional and EBUS-guided TBNA, an anatomy identification of airway nodes, management of airway bleeding, and management of pneumothorax. This course is ideal for clinicians and health-care professionals with specialties in pulmonary, critical care, and intensive care medicine, as well as thoracic surgery.

The program at the Joint CHEST-SGP Congress aims to improve the patient care abilities of every attendee, as well as provide an ideal environment for networking with leaders in your field.

The call for abstracts remains open until January 24, 2017. The abstract topic areas are:

- Airway disease
- Interstitial lung disease
- Sleep/Breathing
- Lung cancer
- Epidemiology/Rehabilitation
- Interventional pneumology
- Pulmonary hypertension
- Basic science
- Thoracic surgery
- Pediatrics

All abstracts must be submitted via the Joint Congress abstracts web portal www.chest-sgp-switzerland2017.org.

CHEST recognizes the value of international outreach, and this Joint Congress advances that initiative. CHEST aims to standardize the patient care across borders and to encourage international collaboration to build the future of chest medicine. To further this mission, an application has been made to the European Accreditation Council for Continuing Medical Education (EACCME®) for CME accreditation of this event. Additionally, an application has been made to the European Board for Accreditation in Pneumology (EBAP) to provide quality assurance and CME for the event.

For more information or to register, visit the CHEST Joint Congress website www.chest-sgp-switzerland2017.org. Early registration ends on March 16, 2017.

In Memoriam

CHEST has been informed of the following members' deaths. We extend our sincere condolences.

Anthony Cosentino, MD, FCCP (January 2016)
Ben Branscomb, MD (July 2016)
Steven Sahn, MD, FCCP (Aug 2016)
Thomas Aldrich, MD (September 2016)
John C. Baldwin, MD, FCCP (September 2016)
David Cugell, MD, FCCP (December 2016)

Adding respiratory rate to triage criteria improves accurate staging of chest trauma patients

BY MICHELE G. SULLIVAN
Frontline Medical News

WASHINGTON – Adding respiratory rate and suspected blunt chest injury to a trauma assessment in the field significantly improved the appropriate triaging of level III trauma patients.

When the assessment specifically evaluated for tachypnea in the setting of blunt chest injury, undertriaging improved by 1.2%, John Yonge, MD, said at the annual clinical congress of the American College of Surgeons.

"When we applied this new criteria to our 10-year study, we identified 661 patients who should have been activated as a level I or level II," but instead were assessed as less critically injured, Dr. Yonge said in an interview. This initial misstep significantly extended the time before patients could have critical surgical procedures and was related to higher mortality among them.

Dr. Yonge, a surgical fellow at Oregon Health & Science University, Portland, and his mentor Martin Schreiber, MD, conducted the retrospective study of 7,880 trauma patients admitted at level III activation from 2004 to 2014. The OHSU trauma system has three activation levels.

• Level I activations are reserved for the most critically injured patients; attending trauma surgeon and anesthesiologist presence is mandatory.

• Level II activations capture moderate to severe injuries; trauma surgeon and respiratory therapist presence is mandated.

• Level III activations are designed to capture patients who do not require an immediate lifesaving intervention; the presence of the trauma surgery chief resident and attending emergency medicine physician is mandatory.


DR. YONGE

Patients were considered undertriaged if they were admitted as level III activations, but then required a critical intervention (chest tube placement, intubation, needle thoracostomy, or intracranial pressure monitoring) in the emergency department or ultimately met level I or II activation criteria.

Among all the level III patients, 466 (6%) were undertriaged: 390 were undertriaged based on the existing level I or II activation criteria, and 76 were considered undertriaged based on the need for a critical intervention.

Most of the undertriaged patients (65%) met criteria for level I activation; the rest should have been triaged as level II patients. Compared with appropriately staged level III patients, mortality among the undertriaged patients was significantly higher (3.2% vs. 0.6%). Undertriaged patients also experienced longer delays before initiation of major emergency surgery: a mean of 147 minutes, compared with 106 minutes for appropriately triaged level I patients and 62 minutes for appropriately triaged level II patients.

Dr. Yonge then looked for clinical measures that would improve triage. Tachypnea (respiratory rate of more than 20 breaths per minute) in the field stood out as a significant factor. Tachypneic patients who had a suspected chest injury were 70% more likely to be undertriaged than were those with a normal respiratory rate. Tachypnea was significantly associated with a diagnosis of flail chest, emergency department intubation, and chest tube placement.

The team then constructed a new triage criterion for patients with suspected chest injury – tachypnea combined with suspected blunt thoracic injury. By applying that model to their study population of level III patients, they determined that the level III undertriage rate would be reduced by 1.2%.

Tying the physiologic marker of tachypnea to a suspected clinical diagnosis is a key factor, Dr. Yonge noted. "Just adding tachypnea doesn't help us. In fact, it would overwhelm us, because a trauma patient could very well be tachypneic because he's experiencing panic. But tying it to a suspected clinical diagnosis gives us a meaningful result."

He confirmed this linkage with an additional analysis. "We looked to see how severely injured these patients were and found that 71% of them had an Abbreviated Injury Score (AIS) to the chest of 3 or more, indicating a severe chest injury. Only 29% had an AIS of 2 or less. So this proves that respiratory rate is a valid triage criterion and can be used to identify patients who need a higher level of trauma care."

The challenge now, Dr. Yonge said, is incorporating the marker into clinical practice. "It doesn't matter how many statistics you do, if you can't educate the prehospital providers in this, it's useless. They are the crux of the trauma system."

Tying the physiologic marker of tachypnea to a suspected clinical diagnosis is a key factor, Dr. Yonge noted. "Just adding tachypnea doesn't help us. In fact, it would overwhelm us ... "

Although national guidelines do recommend assessing respiratory rate as part of field triage, it often isn't recorded or is only estimated, Dr. Yonge said. That's one reason he used the 20-breaths-per-minute cutoff rate. "It doesn't even take a full minute to assess this, but it can make a big improvement in care."

Neither he nor Dr. Schreiber had any financial disclosures.

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Confirmatory CT prevents unnecessary bronchoscopy

BY M. ALEXANDER OTTO
Frontline Medical News

It's probably a good idea to do a repeat CT the morning of a scheduled bronchoscopy to make sure the pulmonary nodule is still there, according to investigators from Johns Hopkins University, Baltimore.

From Jan. 2015 to June 2016, 116 patients there were scheduled for navigational bronchoscopy to diagnose pulmonary lesions found on screening CTs. Eight (6.9%) – four men, four women, with an average age of 50 years – had a decrease in size or resolution of their lesion on confirmatory CT, leading to cancellations of their procedure. The number needed to screen to prevent one unnecessary procedure was 15. For canceled cases, the average time from screening CT to scheduled bronchoscopy was 53 days; for patients who underwent a bronchoscopy, it was 50 days (Ann Am Thorac Soc. 2016 Dec;13[12]:2223-8).

It can take months to schedule a bronchoscopy after a pulmonary nodule is found on CT screening. Once in a while, the investigators and others have found, even suspicious nodules resolve on their own, and patients end up having a bronchoscopy they don't need.

"If there is a significant delay from the initial imaging, practitioners should consider repeat studies before proceeding with the scheduled procedure ... Same-day imaging may decrease unnecessary procedural risk ... The optimal time that should be allowed to pass is difficult to ascertain," said investigators led by Roy Semaan, MD, of the division of pulmonary and critical care medicine at Hopkins.

The team used a newer version of electromagnetic navigation bronchoscopy (Veran Medical Technologies, St. Louis), which requires expiratory and inspiratory CTs the morning of the procedure so software can build a virtual airway model to localize the nodule.

In addition to nodule resolution, same-day CTs might identify disease progression that alters the diagnostic plan of care.

"The most obvious risk associated with repeat CT imaging is the increased radiation exposure to the patient. Patients in our study who received inspiratory and expiratory CT scans ... had a mean exposure of 9.485 mSv, which is not "negligible, but one-time doses at this range are generally considered to be low risk for contributing to the future development of a malignancy," the team said.

The extra cost of a same-day noncontrast chest CT – about $300, the authors said – is more than offset if it cancels "an unnecessary procedure with its associated risks," they said.

Dr. Semaan had no disclosures. Three investigators reported grants and personal fees from Veran.

aotto@frontlinemedcom.com

ANORO is for the once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO, 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 LABA, including vilanterol.**
- **The safety and efficacy of ANORO in patients with asthma have not been established. ANORO is not indicated for the treatment of asthma.**

CONTRAINDICATIONS

- The use of ANORO is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- ANORO 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 ANORO should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this advertisement.

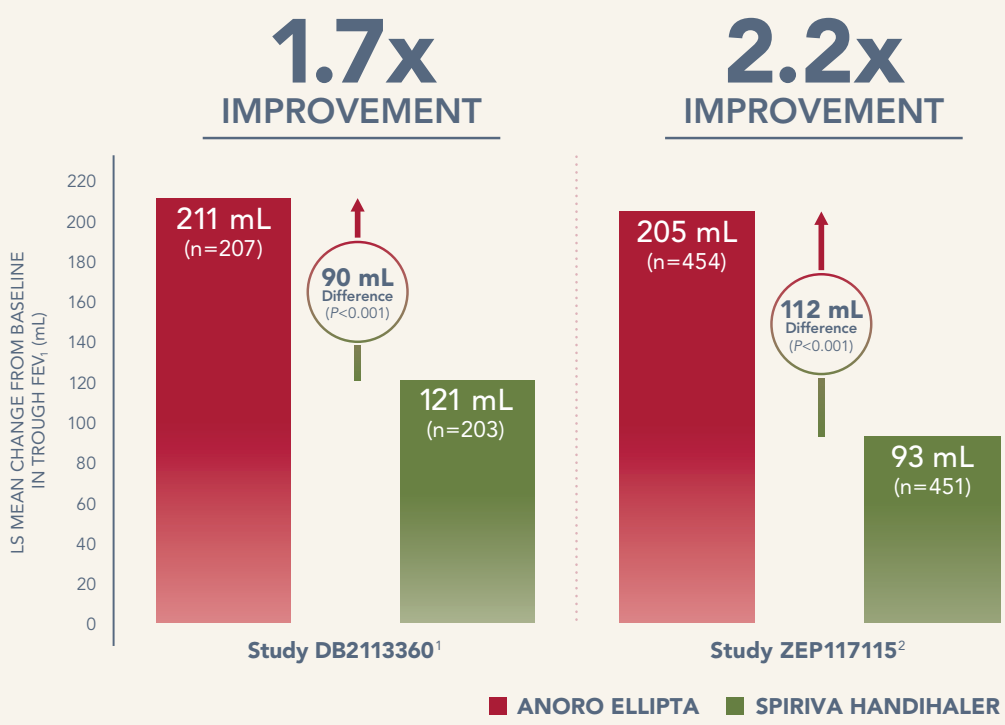
gsk | Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

START STRONG WITH ANORO INSTEAD OF SPIRIVA FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION

SIGNIFICANT IMPROVEMENT IN TROUGH FEV_1 AT DAY 169[1,2]

Studied in patients with moderate or worse COPD (GOLD 2-4)



ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

SPIRIVA HANDIHALER is an anticholinergic for the maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.[3]

FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; LS=least squares.

In a separate study (DB2113374), ANORO ELLIPTA (n=217) compared with SPIRIVA HANDIHALER (n=215) showed a 60-mL difference† (208 mL and 149 mL, respectively), but due to testing hierarchy, statistical significance cannot be inferred.[1]

†Reflects rounding.

DESCRIPTION OF STUDIES[1,2,4]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) were evaluated in 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV_1 range of 46.4% to 47.7% predicted. The studies were not powered to compare the safety profiles of the products.

PRIMARY ENDPOINT: Trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168).

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Caution should be exercised when considering the coadministration of ANORO with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO 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, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

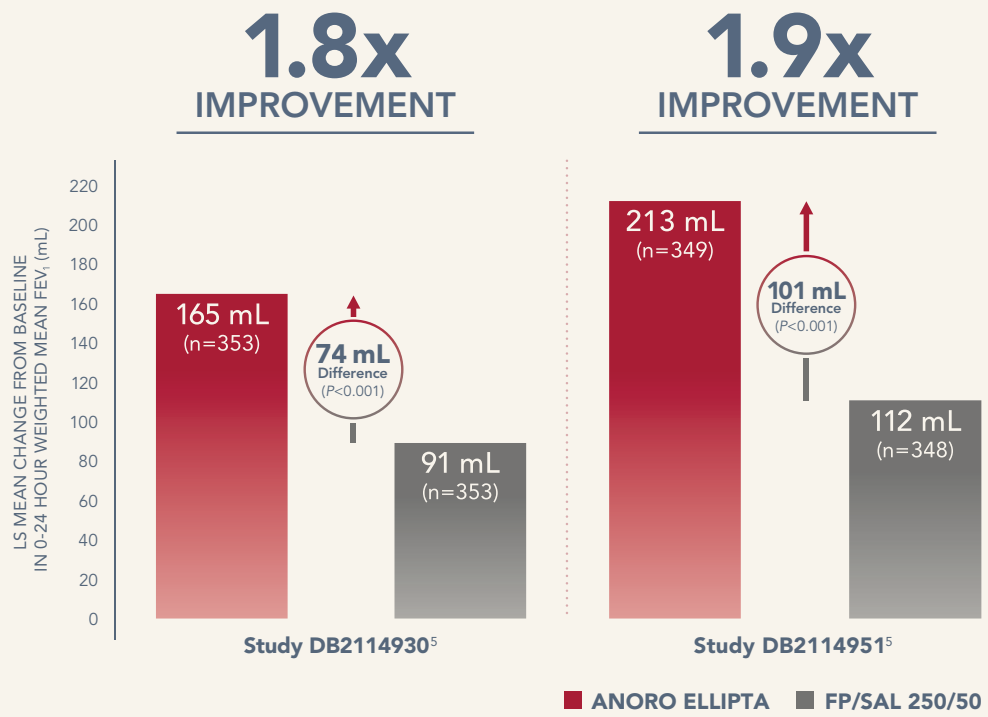
ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity, 2% (1%); muscle spasms, 1% (<1%); neck pain, 1% (<1%); and chest pain, 1% (<1%).
- In addition to the 6-month efficacy trials with ANORO, a 12-month trial evaluated the safety of umeclidinium/vilanterol 125 mcg/25 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and more common than placebo) in subjects receiving umeclidinium/vilanterol 125 mcg/25 mcg were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

START STRONG WITH ANORO INSTEAD OF FP/SAL 250/50 FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION

SIGNIFICANT IMPROVEMENT IN WEIGHTED MEAN FEV_1 (0-24 HOURS) ON DAY 84[5]

Studied in patients with moderate to severe COPD (GOLD 2 or 3)



ANORO ELLIPTA is a combination anticholinergic/LABA for the maintenance treatment of airflow obstruction in patients with COPD.

FP/SAL 250/50 mcg is indicated to reduce COPD exacerbations, whereas ANORO ELLIPTA is not.

FP=fluticasone propionate; SAL=salmeterol.

DESCRIPTION OF STUDIES[4,5]

The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of FP/SAL 250/50 mcg (administered by the DISKUS® inhaler) were evaluated in 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

PRIMARY ENDPOINT: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

Important Safety Information for ANORO ELLIPTA (cont'd)

DRUG INTERACTIONS

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

Please see additional Important Safety Information for ANORO ELLIPTA on the preceding pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA on the following pages.

References: 1. Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med.* 2014;2(6):472-486. **2.** Maleki-Yazdi MR, Kaelin T, Richard N, et al. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med.* 2014;108(12):1752-1760. **3.** SPIRIVA HANDIHALER [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016. **4.** Data on file, GSK. **5.** Donohue JF, Worsley S, Zhu C, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015;109(7):870-881.

There's more to know about ANORO at StartWithANORO.com

ANORO ELLIPTA was developed in collaboration with Theravance

ANORO® ELLIPTA®
(umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

BRIEF SUMMARY

ANORO® ELLIPTA®
(umeclidinium and vilanterol inhalation powder), for oral inhalation
The following is a brief summary only; see full prescribing information for complete product information.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA *[see Warnings and Precautions (5.1)]*.

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

1 INDICATIONS AND USAGE
ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS
The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.6), Description (11) of full Prescribing Information]*.

5 WARNINGS AND PRECAUTIONS
5.1 Asthma-Related Death
Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; 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 ANORO ELLIPTA.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.
5.2 Deterioration of Disease and Acute Episodes
ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.
ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.
COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.
5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta$_2$-Agonists
ANORO ELLIPTA 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 ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full Prescribing Information]*.
5.5 Paradoxical Bronchospasm
As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.
5.6 Hypersensitivity Reactions
Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA *[see Contraindications (4)]*.
5.7 Cardiovascular Effects
Vilanterol, like other beta$_2$-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) of full Prescribing Information]*. If such effects occur, ANORO ELLIPTA 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, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
5.8 Coexisting Conditions
ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.
5.9 Worsening of Narrow-Angle Glaucoma
ANORO ELLIPTA 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 if any of these signs or symptoms develops.
5.10 Worsening of Urinary Retention
ANORO ELLIPTA 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 if any of these signs or symptoms develops.
5.11 Hypokalemia and Hyperglycemia
Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS
LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.
6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).
Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions with ANORO ELLIPTA with ≥1% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	ANORO ELLIPTA (n = 842) %	Umeclidinium 62.5 mcg (n = 418) %	Vilanterol 25 mcg (n = 1,034) %	Placebo (n = 555) %
Infections and infestations				
Pharyngitis	2	1	2	<1
Sinusitis	1	<1	1	<1
Lower respiratory tract infection	1	<1	<1	<1
Gastrointestinal disorders				
Constipation	1	<1	<1	<1
Diarrhea	2	<1	2	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	2	<1	2	1
Muscle spasms	1	<1	<1	<1
Neck pain	1	<1	<1	<1
General disorders and administration site conditions				
Chest pain	1	<1	<1	<1

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.
12-Month Trial: In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.
6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of ANORO ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to ANORO ELLIPTA or a combination of these factors.
Cardiac Disorders
Palpitations.
Immune System Disorders
Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.
Nervous System Disorders
Dysgeusia, tremor.
Psychiatric Disorders
Anxiety.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers.

However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, 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 ANORO ELLIPTA with non–potassium-sparing diuretics.

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA 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 ANORO ELLIPTA.

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 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.

Nonteratogenic Effects: *Umeclidinium:* There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA

It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

Umeclidinium

It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

Vilanterol

It is not known whether vilanterol is excreted in human breast milk. However, other beta$_2$-agonists have been detected in human milk.

8.4 Pediatric Use

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 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

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed. *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Renal Impairment

There were no significant increases in either umeclidinium 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 case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for the individual components, umeclidinium and vilanterol, as described below.

Umeclidinium

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

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 that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine 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$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

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

Do Not Use Additional Long-Acting Beta$_2$-Agonists: Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and contact their healthcare provider right away.

Risks Associated with Beta-Agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Worsening of Narrow-Angle Glaucoma: Instruct patients to 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 if any of these signs or symptoms develops.

Worsening of Urinary Retention: Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

ANORO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Recovery path complicated with post-trauma VTE

BY DOUG BRUNK
Frontline Medical News

CORONADO, CALIF. – Patients who develop a venous thromboembolism (VTE) following severe hemorrhage are more susceptible to complications, compared with their counterparts who do not; they also exhibit hypercoagulability and enhanced platelet function at admission, and have delayed recovery of coagulation and platelet function following injury.

Those are the key findings from a secondary analysis of data from the Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial, which randomized 680 severely injured trauma patients from 12 level I trauma centers to receive 1:1:1 or 1:1:2 ratios of plasma to platelets to red blood cells (JAMA 2015;313[5]:471-82). "The prevention of VTE following traumatic injury is an ongoing challenge," Belinda H. McCully, PhD, said at the annual meeting of the Western Surgical Association. "Despite prophylaxis, about 25% of patients present with VTE, which is associated with higher complications and an increased risk for mortality. Common risk factors for mortality include age, body mass index, extremity injury, and immobility, but the precise mechanisms that contribute to VTE development are not well understood. We do know that the three main factors contributing to thrombosis include static flow, endothelial injury, and hypercoagulability. Clinically, coagulation is the most feasible factor to assess, mainly through the use of conventional coagulation tests, thromboelastography, platelet levels, and platelet function assays." However, she continued, severe hemorrhage can lead to a hypocoagulable state that is further exacerbated by hemodilution, acidosis, and hypothermia, creating traumatic-induced coagulopathy. "Despite this hypocoagulable state, VTEs are still present in this patient population."

FRONTLINE MEDICAL NEWS
Preventing VTE after trauma is a challenge, noted Dr. McCully.

Dr. McCully of the division of trauma, critical care, and acute care surgery in the department of surgery at Oregon Health & Science University, Portland, and her associates hypothesized that enhanced, earlier recovery of coagulation function is associated with increased VTE risk in severely injured trauma patients. To test this hypothesis, they conducted a secondary analysis of the PROPPR database, excluding patients who received anticoagulants, to rule out any bias against VTE development, as well as patients who died within 24 hours, to reduce the survival bias. This left 558 patients: 475 who did not develop a VTE, and 83 who did (defined as those who developed deep vein thrombosis or pulmonary embolism). Patient characteristics of interest included age, sex, BMI, mechanism of injury, and injury severity, as well as the transfusion group, the type of blood products given, and the percentage of patients given procoagulants. The investigators also assessed length of stay and complication incidence previously defined by the trial. During the trial, blood samples were taken from admission up to 72 hours and were used to assess both whole blood coagulation using thromboelastography and platelet function using the Multiplate assay.

Dr. McCully reported that VTE patients and non-VTE patients demonstrated similar admission platelet function activity and inhibition of all platelet function parameters at 24 hours (*P* less than .05).

The onset of platelet function recovery was delayed in VTE patients, specifically for arachidonic acid, adenosine-5'-diphosphate, and collagen. Changes in thromboelastography, clot time to initiation, formation, rate of formation, and strength and index of platelet function from admission to 2 hours indicated increasing hypocoagulability (*P* less than .05) but suppressed clot lysis in both groups. Compared with patients in the non-VTE group, the VTE group had lower mortality (4% vs. 13%) but increased total hospital days (a mean of 30 vs. 16; *P* less than .05).

Adverse outcomes were also more prevalent in the VTE group, compared with the non-VTE group, and included systemic inflammatory response syndrome (82% vs. 72%), acute kidney injury (36% vs. 26%), infection (61% vs. 31%), sepsis (60% vs. 28%), and pneumonia (34% vs. 19%; *P* less than 0.05 for all associations). Conversely, regression analysis showed that VTE was associated only with total hospital days (odds ratio, 1.12), while adverse events were similar between the two groups. "From this we can conclude that VTE development following trauma may be attributed to hypercoagulable thromboelastography parameters and enhanced platelet function at admission, and compensatory mechanisms in response to a delayed recovery of coagulation and platelet function," Dr. McCully said.

She acknowledged certain limitations of the study, including the fact that it was a secondary analysis of prospectively collected data. "We also plan to assess plasma markers of clot strength and fibrinolysis, which is an ongoing process," she said. "Despite excluding patients that died within 24 hours, there was still a survival bias in the VTE group."

The PROPPR study was supported by the National Heart, Lung, and Blood Institute and by the Department of Defense.

Dr. McCully reported having no relevant financial disclosures.

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Steroids could reduce death rate for some TB patients

BY JENNIE SMITH
Frontline Medical News

Tuberculosis patients admitted to intensive care units with acute respiratory failure had significantly better survival at 90 days after treatment with corticosteroids and anti-TB drugs, compared with patients not treated with the steroids, according to a retrospective study.

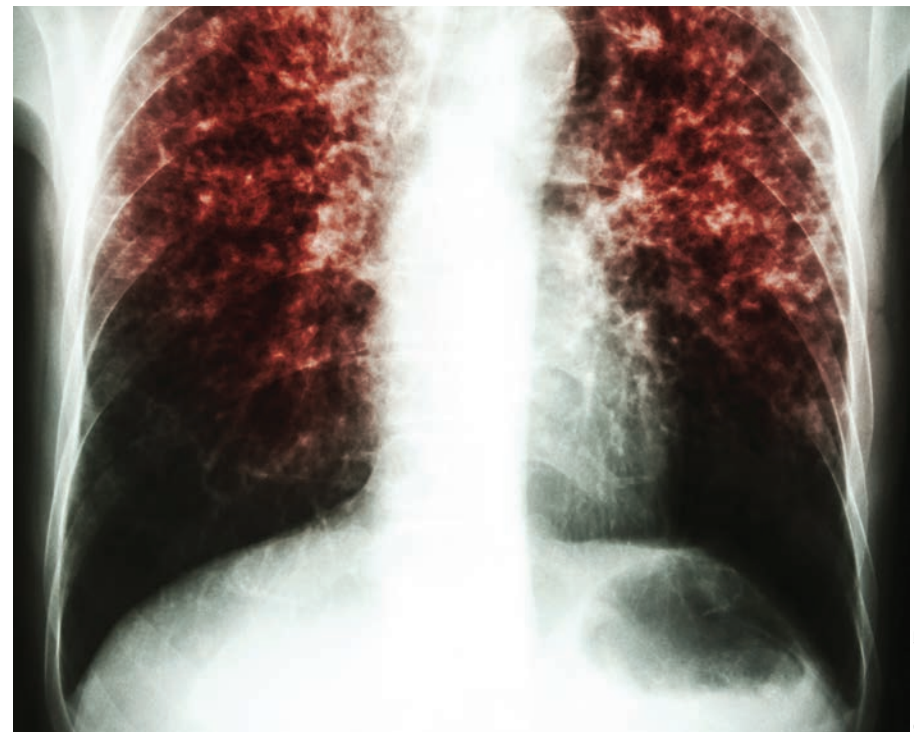
An adjusted inverse probability of treatment weighted analysis using propensity scores revealed corticosteroid use to be independently associated with a significantly reduced 90-day mortality rate (OR = 0.47; 95% CI, 0.22-0.98). This statistical approach was used because it reduces selection bias and other potential confounding factors in a way that a multivariate analysis cannot, wrote Ji Young Yang, MD, of Busan (South Korea) Paik Hospital and Inje University College of Medicine in Busan.

The study involved the examination of records of 124 patients (mean age 62, 64% men) admitted to a single center over a 25-year period ending in 2014. Of these, 56.5% received corticosteroids, and 49.2% of the cohort died within 90 days.

Mortality rates were similar between the steroid-treated and non–steroid-treated groups (48.6% and 50%, respectively), and unadjusted 90-day mortality risk was not affected by steroid administration (odds ratio, 0.94; 95% CI, 0.46-1.92; $P = .875$), reported Dr. Yang and colleagues (Clin Infect Dis. 2016 Sep 8. doi: 10.1093/cid/ciw616).

The investigators acknowledged that their study was limited by various factors, including its small size, its use of data from a single center, and its lack of a standardized approach to steroid treatment.

"Further prospective randomized controlled trials will therefore be necessary to clarify the role of steroids in the management of these patients," they wrote in their analysis. However, Dr. Yang and colleagues argued, in acute respiratory failure – a rare but dangerous complication in TB – "corticosteroids represent an attractive option because they can suppress cytokine expression and are effective in managing the inflammatory complications of extrapulmonary tuberculosis. Moreover, corticosteroids have been recently been shown to reduce mortality or treatment failure in patients with tuberculosis or severe pneumonia."



STOCKDEVIL/THINKSTOCK

***Mycobacterium tuberculosis* infection (pulmonary tuberculosis)**

Robert C. Hyzy, MD, FCCP, director of the critical care medicine unit at the University of Michigan, Ann Arbor, said the findings "should be considered hypothesis generating. "Clinicians should wait for prospective validation of this observation before considering the use of corticosteroids in hospitalized patients with tuberculosis," he added.

Dr. Yang and colleagues disclosed no conflicts of interest or outside funding for their study.

More restrictive hemoglobin threshold advised

BY BIANCA NOGRADY
Frontline Medical News

New guidelines on red blood cell blood transfusion recommend a restrictive threshold in which transfusion is not indicated until the hemoglobin level is 7-8 g/dL for most patients, finding that it is safe in most clinical settings.

The updated clinical practice guidelines on transfusion thresholds and storage from the AABB (formerly known as the American Association of Blood Banks), also note that red blood cell units can be used at any time within their licensed dating period, rather than a preference being given to fresher units less than 10 days old.

The guidelines, published online Oct. 12 in JAMA, are an update of the 2012 transfusion guidelines, and are a response to a more than doubling of the number of patients since enrolled in randomized controlled trials of red blood cell transfusions.

The AABB's clinical transfusion medicine committee, led by Jeffrey L. Carson, MD, of Robert Wood Johnson Medical School, New Brunswick, N.J., analyzed data from 31 randomized controlled trials of 12,587 participants, which compared restrictive transfusion thresholds of 7-8 g/dL to more liberal thresholds of 9-10 g/dL.

This analysis showed that the use of restrictive transfusion protocols was associated with an absolute difference in 30-day mortality of three fewer deaths compared to the more liberal thresholds. There was no significant difference in 30-day mortality in trials that compared a threshold of 8-9 g/dL to a threshold of less than 7 g/dL (JAMA 2016, Oct 12. doi: 10.1001/jama.2016.9185).

"For all other outcomes evaluated, there was no evidence to suggest that patients were harmed by restrictive transfusion protocols, although the quality of the evidence was low for the outcomes of congestive heart failure and rebleeding," the authors reported.

Based on these findings, they recommended a restrictive red blood cell transfusion threshold, in which transfusion is not indicated until the hemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients.

However for patients undergoing orthopedic or cardiac surgery, or those with preexisting cardiovascular disease, they advised a threshold of 8 g/dL for initiating a red blood cell transfusion.

They also stressed that these recommendations did not apply to patients with acute coronary syndrome, those with severe thrombocytopenia, those treated for hematologic or oncologic disorders who at risk of bleeding, and those with chronic transfusion–dependent anemia, citing a lack of quality randomized controlled trial evidence.

The guideline authors examined the issue of the optimal length of time that red blood cell units should be stored, pointing out that there is currently no formal guidance on the optimal period of red blood cell storage prior to transfusion.

While units of red blood cells can be stored for up to 42 days, the committee said there was some evidence that longer storage may be associated with adverse transfusion outcomes.

"The RBCs stored for longer periods have decreased ability to deliver oxygen due to decreased levels of 2,3-diphsophoglycerate, decreased nitric oxide metabolism, alterations of the RBC membrane leading to increased rigidity, and increased RBC endothelial adherence," they wrote.

Despite this, the review of 13 randomized controlled trials examining the effect of storage duration found no evidence that fresher units had any impact on mortality compared to standard issue units, nor were there any more adverse events with the standard issue units.

The absolute difference in 30-day mortality was four more deaths per 1,000 with fresher blood, and there was a higher risk of nosocomial infections among patients who received fresher red blood cell units although the authors said the quality of evidence was low.

They therefore recommended that no preference be given to fresher red blood cell units, and that all patients be treated with units chosen at any point within their licensed dating period.

Guideline development was supported by AABB. Four authors declared grants, fees, stock options or consultancies from pharmaceutical companies, but no other conflicts of interest were declared.

VIEW ON THE NEWS

Nirmal S. Sharma, MD, FCCP, comments: These recommendations are very helpful and are now part of standard ICU care in several centers. Our experience in clinical practice has shown that even patients supported with extracorporeal membrane oxygenation (ECMO) for acute lung failure or as a bridge to lung transplantation on VV ECMO can safely tolerate a lower transfusion threshold (7-8g/dL.) Future well-designed trials are needed to advocate its safety in patients supported with extracorporeal life support technologies.

INDEX OF ADVERTISERS

Macrolide monotherapy works in some NTM lung disease

Most with NTM lung disease plus Mycobacterium massiliense *were successfully treated*

BY JENNIE SMITH
Frontline Medical News

FROM CHEST

Patients with cystic fibrosis or bronchiectasis and one form of *Mycobacterium abscessus* disease can be successfully treated with long-term oral macrolide monotherapy following short-term intravenous combination antibiotic therapy, a Korean research team has shown.

The *M. abscessus* complex is implicated in between a fifth and half of all cases of lung disease caused by nontuberculous mycobacteria (NTM). Though treatment is notoriously difficult and prolonged in all NTM lung disease, one subspecies of *M. abscessus* – *M. massiliense* – lacks the active gene needed for developing resistance to macrolide-based antibiotics, making it potentially more readily treated.

In research published in CHEST, Won-Jung Koh, MD, of Samsung Medical Center and Sungkyunkwan University in Seoul, South Korea, and colleagues, sought to determine the optimal treatment protocol for patients with massiliense disease (Chest. 2016 Dec;150[6]:1211-21). They identified 71 patients with massiliense disease who had initiated antibiotic treatment between January 2007 and December 2012. These patients were part of an ongoing prospective cohort study on NTM lung disease. The first 28 patients in the study were hospitalized for 4 weeks and treated with intravenous amikacin and cefoxitin along with oral clarithromycin and a fluoroquinolone. Following discharge, these patients remained on the oral agents for 24 months.

Two years into the study, the protocol changed, and the next 43 patients were treated with a 2-week course of intravenous amikacin and cefoxitin along with the oral agents. In some patients, azithromycin, which came into use in Korea for NTM lung disease in 2011, replaced a fluoroquinolone. After discharge, all patients stayed on the oral mac-

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rolides (with seven also taking a fluoroquinolone) until their sputum cultures were negative for 12 months.

For the patients treated for 4 weeks, the response rates after 12 months of treatment were 89% for symptoms, 79% for computed tomography, and 100% for negative sputum cultures. In the patients treated for 2 weeks, they were 100%, 91%, and 91%, respectively. None of these differences between the two groups were statistically significant. Median total treatment duration, however, was significantly shorter – by nearly a year – in the 2-week plus macrolide monotherapy group than in the other group of patients (15.2 months vs. 23.9 months, *P* less than .001).

Acquired macrolide resistance developed in two patients in the group who received a 2-week course of intravenous amikacin and cefoxitin along with the oral agents, including one case of high-level clarithromycin resistance. Genotyping revealed reinfection with different strains of *M. massiliense*.

"[Oral] macrolide therapy after an initial 2-week course of combination antibiotics, rather than long-term parenteral antibiotics, might be effective in most patients with *M. massiliense* lung disease," Dr. Koh and colleagues wrote, noting that multicenter randomized trials would be needed "to assess the efficacy" of the findings.

The Korean government funded Dr. Koh and colleagues' study. None of the authors disclosed conflicts of interest.

VIEW ON THE NEWS

"Risk/benefit balance" does not favor macrolide monotherapy use

"In this study by Koh et al., it is gratifying that most patients had a favorable microbiologic outcome. It is also somewhat surprising that only two patients developed acquired macrolide resistant *M. abscessus* subsp *massiliense* isolates. While the absolute number is low, for those two individuals, the consequences of developing macrolide resistance are far from trivial. They have transitioned from having a mycobacterial infection that is relatively easy to treat effectively to a mycobacterial infection that is not," David E. Griffith, MD, FCCP, and Timothy R. Aksamit, MD, FCCP, wrote in an editorial published in the December issue of CHEST (Chest. 2016 Dec;150[6];1177-8).

The authors noted that they "enthusiastically applaud and acknowledge the prolific and consistently excellent work done by the group in South Korea, but we cannot endorse the widespread adoption of macrolide monotherapy for" this patient group. "In our view, the risk/benefit balance of this approach does not favor macrolide monotherapy even though the majority of patients in this study were adequately treated."

Dr. Griffith is professor of medicine at University of Texas Health Science Center, Tyler, and Dr. Aksamit is a consultant on pulmonary disease and critical care medicine at the Mayo Clinic, Rochester, Minn. They disclosed no conflicts of interest.

CORRECTION

On page 7 of the November issue of CHEST Physician, the third sentence of the fourth paragraph contained an error. The sentence should have read, "They were randomized to infusions of reslizumab 3.0 mg/kg or placebo given once every 4 weeks for 16 weeks."

Blood assay rapidly identifies lung cancer mutations

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – A newer blood test (GeneStrat from Biodesix) identified genetic mutations in lung tumors in about 24 hours, allowing for an early start of mutation-specific chemotherapy, in an investigation from Gundersen Health System in La Crosse, Wis.

Researchers drew blood samples when they performed biopsies on 84 patients with highly suspicious lung nodules and submitted both blood and tissue for mutation analysis. The blood was analyzed by Biodesix, the maker of GeneStrat, a commercially available digital droplet polymerase change reaction assay launched in 2015. The company sent the results back in an average of 24.1 hours, and all within 72 hours. The mutation results from tissue analysis took 2-3 weeks.

Fifteen patients (18%) had epidermal growth factor receptor (EGFR) mutation, echinoderm microtubule-associated-protein-like 4 and anaplastic lymphoma kinase (EML4-ALK) gene fusion, or K-Ras protein gene mutation. Those with EGFR or EML4-ALK mutations were candidates for targeted therapy. Compared with tissue testing, the blood assay had a sensitivity of 88% and a specificity of 99%. The tissue testing picked up two mutations missed by blood testing. One of the two mutations is rare and was not included in the blood assay. Meanwhile, the assay caught a mutation missed on tissue analysis.

"I was surprised" by the results. "I didn't expect to have that level of concordance [96%] between blood and tissue. I thought we would miss a lot more with blood," but tissue and blood testing were "nearly equivalent," said lead researcher and interventional pulmonologist Jennifer Mattingley, MD, at the annual meeting of the American College of Chest Physicians.


DR. MATTINGLEY

She and her colleagues are now routinely using GeneStrat to guide initial lung cancer therapy. "[The turnaround time] allows us to have [the mutation status] when oncologists meet with patients for the very first time," she said.

It "definitely" makes a difference. "If you have an actionable mutation and there's a targeted chemotherapy" – such as erlotinib (Tarceva) for epidermal growth factor receptor mutation patients – it can be started right out of the gate. "Time to treatment is very important," not just psychologically for patients but also for them to have the best chance against the tumor. The sooner "we can start a targeted therapy," the better outcomes are likely to be, Dr. Mattingley said.

When mutation status is delayed, patients might be started "on the wrong therapy upfront, and it's really hard to back up and start over again," she said.

"Once we give patients a diagnosis of lung cancer, the next thing they should hear right away is how we are going to attack it. We felt strongly [that there was a] need to look at this to see if we could truly expedite the time from diagnosis to treatment. We

Continued on following page

Half of MPE patients received unneeded treatment

BY M. ALEXANDER OTTO
Frontline Medical News

AT CHEST 2016

LOS ANGELES – About half of patients with symptomatic malignant pleural effusions at McGill University Health Centre in Montreal had unnecessary procedures and hospital admissions before definitive treatment with chemical pleurodesis or indwelling pleural catheters, according to researchers.

Instead of chest taps to relieve symptoms followed by referrals for definitive treatment, some patients got chest tubes – without pleurodesis – after presenting to the emergency department and being referred to radiology; they were then admitted to the hospital for a few days while the tubes were in place. In short, cancer patients were wasting what time they had left on medical care they didn't need, and incurring unnecessary costs, said lead investigator Benjamin Shieh, MD, formerly at McGill but now an interventional pulmonology fellow at the University of Calgary.

McGill is a tertiary care center able to perform both definitive procedures, so "we should be a center of excellence. I imagine there are similar situations" at other hospitals, especially those without the resources of McGill, Dr. Shieh said at the annual meeting of the American College of Chest Physicians.

McGill has taken several steps to address the problem, including early ED referral to the pulmonology service and discouraging radiology from placing chest tubes for malignant pleural effusions (MPE). "I think we can avoid a big proportion of hospitalizations for MPE, and certainly a proportion of repeat [ED] visits," said senior author Anne Gonzalez, MD, an attending pulmonologist at McGill.

The investigators looked into the issue after noting that a significant number of patients with MPE had been hospitalized with chest tubes. They reviewed 72 symptomatic MPE cases in 69 patients treated in 2014 and 2015. The patients were 70 years old, on average, and about 60% were women. Lung and breast were the most common cancers.


DR. SHIEH


DR. GONZALEZ

Management was ideal in 36 cases (50%), meaning that, prior to definitive treatment, patients had no more than two pleural taps for symptom relief, no more than one ED visit, no chest tubes without pleurodesis, and no hospitalizations. "We thought this would be reasonable to try to achieve for MPE," since there's no definition of ideal management, Dr. Shieh said.

Nonideal patients had a mean of 2.5 pleural procedures – almost twice the number in the ideal group – before definitive palliation, with no respiratory consult beforehand. Chest tubes were placed in 27 cases (38%) for an average of 3.7 days; 28 patients (39%) were hospitalized. Nonideal patients were far more likely to present first to the ED, and ED presentations were more likely to get chest tubes and be admitted. All the cases were eventually treated definitively, 68 with indwelling pleural catheters and 4 by thoracoscopic talc insufflation. Time from initial presentation to definitive palliation was about 1 month in both groups. The investigators didn't consider rate of effusion recurrence, which might help explain why the ideal group wasn't treated sooner; they might not have needed it. The higher number of ED visits in the nonideal group suggests that they may have had quicker recurrences, and should have been treated sooner, Dr. Gonzalez said.

The patients were 70 years old, on average, and about 60% were women. Lung and breast were the most common cancers.

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Continued from previous page

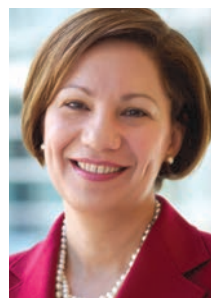
believe our patients should have no sleepless nights," Dr. Mattingley said.

There's usually not much tissue left after genetic work-up to send into a clinical trial, but using blood to identify mutations "may allow us to conserve our tissue block for future trials," noted Dr. Mattingley, who is a speaker for GeneStrat's maker, Biodesix.

aotto@frontlinemedcom.com

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: The results of this study are very promising. The high concordance between liquid biopsies and tissue biopsies as well as the short turnaround time for the results of the liquid biopsies makes a big difference in terms of getting patients started on appropriate therapy sooner rather than later. We need additional studies to find out if liquid biopsies will be good for detection of other molecular alterations such as ROS-1 and EGFR acquired mutation T790M.



Counseling, shared decision-making visit boosts knowledge of lung cancer risks

BY JIM KLING
Frontline Medical News

FROM CHEST

A counseling and shared decision-making visit improved patient knowledge of the eligibility criteria, benefits, and potential risks of lung cancer screening via a low-radiation chest CT scan.

The Centers for Medicare & Medicaid Services has added the type of visit addressed in this study to Medicare's preventive services benefits for individuals meeting certain criteria, but no previous study had looked at how the implementation of such a visit impacted a patient's knowledge and understanding.

Subjects in this study were initially quizzed for knowledge about screening criteria, hazards, and benefits, and then underwent the counseling program. They were tested again immediately after the session, and then 1 month later.

The researchers noted significant improvement in all questions before and after a counseling session ($P = .03$ to P less than .0001). Those improvements lessened at 1 month, but were still higher than precounseling scores.

The percentages of participants who knew the age criteria for lung cancer screening before counseling, immediately after counseling, and 1 month after counseling, for example, were 8.8% (11 patients), 59.2% (74 patients), and 21.4% (24 patients), respectively. The percentage of participants able to identify at least one of the potential hazards of screening increased by a similar amount immediately after receiving counseling, as did the percentage of participants able to identify the age criteria for lung cancer screening immediately after receiving counseling. The percentages of patients able to identify at least one of the potential hazards of screening were 38.4% before counseling and 90.4% immediately after receiving counseling. One month following counseling, the percentage of patients with such knowledge remained fairly high, dropping to 78.6%.

The researchers developed a centralized counseling and shared decision-making visit that included a narrated slide show and individualized risk assessment. They approached 423 consecutive patients who had been identified by their primary care provider or a specialist as potential candidates for screening. Of those 423 patients, 125 agreed to participate in the study (Chest. 2016 Nov 1. doi: 10.1016/j.chest.2016.10.027).

The session delivered expected improvements in patient knowledge, but there were some surprises. "The starting point of knowledge was perhaps less than we would have anticipated, and the gains, though very substantial, weren't perfect," said Peter J. Mazzone, MD, MPH, FCCP, who led the study, in an interview.

The drop in knowledge at 1 month suggests that the information needs to be reinforced, possibly each time patients come in for an annual screening visit, added Dr. Mazzone, who is also director of the lung cancer screening program at the Cleveland Clinic.

Counseling sessions can also help convince patients to quit smoking, if tobacco use is a concern. "It's not appropriate to screen for lung cancer without making a commitment to try to quit," said David Grossman, vice chair of the US Preventive Services Task Force and a senior investigator at the Group Health Research Institute, Seattle, in an interview.

This story's sources reported no financial disclosures.

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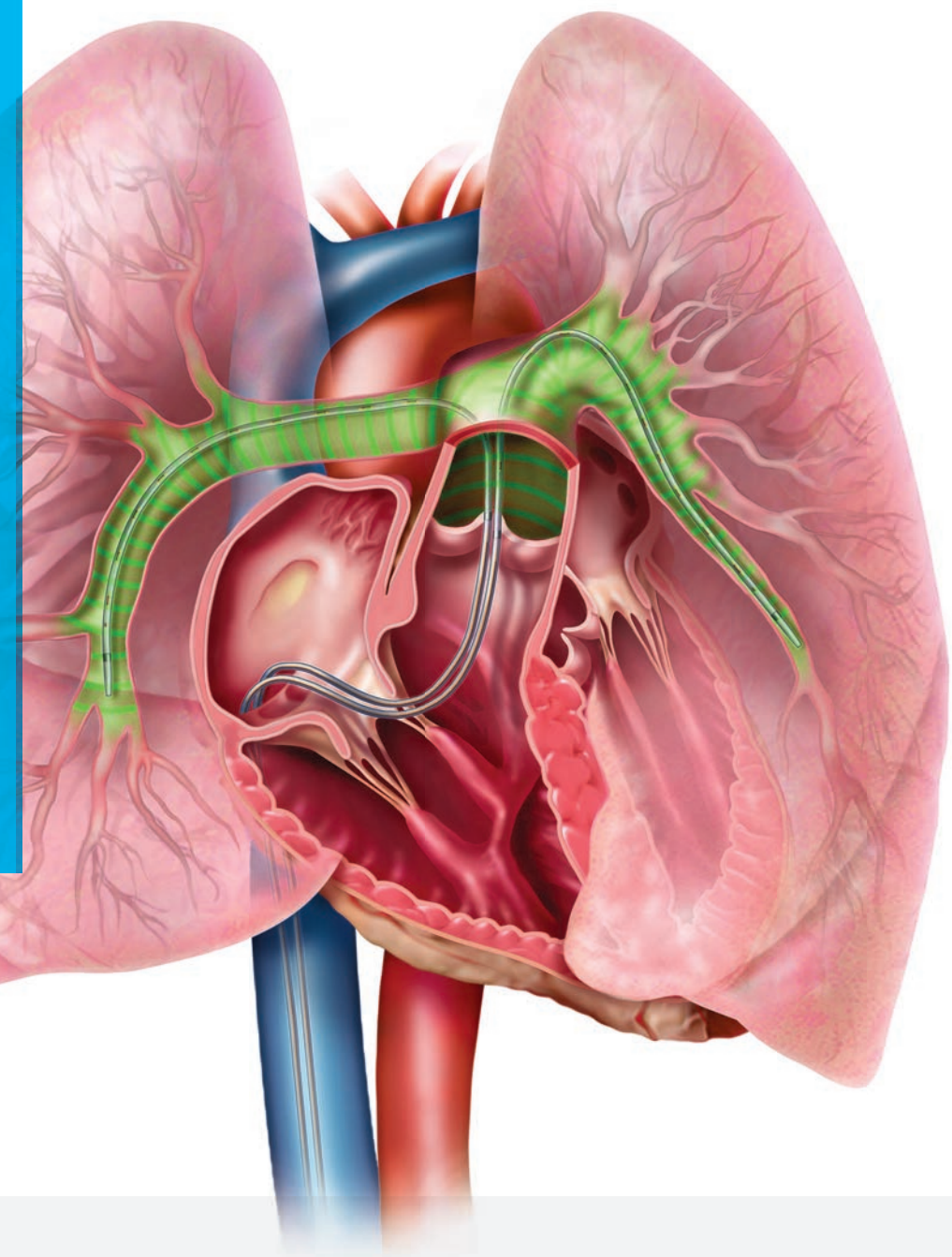
You really don't take my breath away.

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).*

2 *Braaten, J et al., Thromb Haemost 1997;78:1063-8; Francis, C et al. Ultrasound in Medicine and Biology 1995; 21(3):419-424; Soltani, A et al., Physics in Medicine and Biology 2008; 53:6837-6847*

3 *Kucher, N., et al., Circulation, Vol. 129, No. 4, 2014, 479–486.*

4 *Piazza, G., et al., American College of Cardiology 63rd Annual Scientific Session, Wash D.C., March 30, 2014.*

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:** ***Peripheral Vasculature:*** The EkoSonic® Endovascular Device, consisting of the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic™ Device (MSD), is intended for controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature. All therapeutic agents utilized with the EkoSonic® Endovascular System should be fully prepared and used according to the instruction for use of the specific therapeutic agent. ***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.

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