

# CHEST<sup>®</sup> Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



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Screen those with qualifying risk factors and histories for COPD, Dr. John Studdard advises. See commentary on page 7.

## USPSTF nixes general screening for COPD

BY DOUG BRUNK  
Frontline Medical News

There is no apparent benefit to screening for chronic obstructive pulmonary disease in asymptomatic patients, a new recommendation from the U.S. Preventive Services Task Force (USPSTF) concludes.

The recommendation statement, which was published in the April 5 edition of JAMA, meets Grade D criteria, which the task force defines as having “moderate or high certainty that the service has no benefit or that the harms outweigh the benefits.”

Led by Dr. Albert L. Siu of the Icahn School of Medicine

at Mount Sinai, New York, the 16-member task force “found no studies that directly assessed the effects of screening for COPD [chronic obstructive pulmonary disease] in asymptomatic adults on morbidity, mortality, or health-related quality of life,” they wrote (JAMA. 2016 Apr; 315[13]:1372-7).

“The USPSTF also found no studies that examined the effectiveness of screening on relevant immunization rates.” The five studies identified that assessed the effects of screening on smoking cessation “primarily examined the incremental value of adding spirometry testing to existing smoking cessation

See USPSTF • page 7

## NIV, high-flow oxygen reduced risk of reintubation

Data expand population that benefits.

BY KATIE WAGNER  
LENNON  
Frontline Medical News

Extubated patients who either received non-invasive ventilation (NIV) therapy or high-flow nasal cannula oxygen had a lower risk of reintubation, compared with extubated patients who received some form of standard oxygen therapy, according to the results of two multicenter, randomized clinical trials published online in JAMA.

Participants in one of the studies, which included abdominal surgery patients diagnosed with respiratory failure within 7 days follow-

ing surgery, either received NIV or standard oxygen therapy for 30 days or until ICU discharge, whichever came first. While NIV has been effectively used to treat nonsurgical patients with acute exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema, there is no evidence to support the use of NIV in surgical patients with hypoxemic acute respiratory failure after abdominal surgery, according to Dr. Samir Jaber of the Saint Eloi University Hospital and Montpellier School of Medicine, both in Montpellier, France,

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## Antacids did not slow IPF

BY KATIE WAGNER  
LENNON  
Frontline Medical News

Idiopathic pulmonary fibrosis (IPF) progressed at similar rates in patients who did and did not receive antacid therapy, based on a post hoc analysis of 52-week data from patients in three placebo-controlled trials.

“We found no association between antacid therapy and progression-free survival, mortality, or adverse events, reported Dr. Michael Krueter of the University of Heidelberg, Germany, and his colleagues (Lancet Respir Med. 2016 Mar 31;S2213-2600[16]00067-9). Further, patients who took antacids and had less than 70%

forced vital capacity (FVC) had higher rates of pulmonary and nonpulmonary infections than did patients who did not receive antacid therapy.

“Long-term double-blind randomized studies are urgently needed to further investigate the potential benefit (and possible harms)

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# Antacid use not linked to deaths

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of antacid therapy in patients with different stages of IPF, especially those with advanced disease," the researchers said.

The findings challenge the conditional recommendation for antacid use in the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines on the treatment of IPF. That advice was based on previous retrospective studies that indicated antacid users had slower IPF progression, fewer acute exacerbations, and improved survival compared to patients who did not take antacids.

The new study looked at IPF patients in the placebo groups in three large, phase III trials of pirfenidone. In the placebo groups of those stud-

ies, 291 patients were receiving antacid therapy and 333 patients were not receiving antacid therapy at baseline. At 1 year, the rates of disease progression in the placebo group were not significantly different – 38% in the antacid users and 42% in those not using antacids. Disease progression was the composite endpoint of death, an absolute FVC decrease of at least 10%, and a decrease of 50 meters or more in the 6-minute walk distance (6MWD). In both groups of patients, the rates of all-cause mortality were also similar.

The risk of death from IPF at 1 year also was not significantly different; 3.9% for antacid users and 5.2% for those not using antacids.

When patients were grouped on the basis of FVC at baseline – either less than 70% FVC or at least 70% FVC or greater – little or no difference was seen in disease mortality, disease progression, changes in FVC, 6MWD, and all-cause hospital admission between patients who received antacids and those who did not receive antacids at baseline.

Prior to stratification by baseline FVC, the rates of all-cause hospital admissions, gastrointestinal adverse effects, infections, and pulmonary

infections were similar for the two groups of patients. At 52 weeks, however, infections and pulmonary infections were significantly higher in patients who received antacid therapy at baseline compared with those patients who did not receive antacids at baseline (74% vs. 62%;  $P = .0174$  and 14% vs. 6%;  $P = .0214$ , respectively).

Unlike the patients in the previous retrospective studies, few patients in the placebo arms of the clinical trials had advanced IPF and low FVC, the researchers noted. All had IPF that had been diagnosed within 48 months of entering a trial, no evidence of improvement in disease

*Continued on following page*

# DNA modifications seen in smokers' newborns

BY KATIE WAGNER LENNON  
*Frontline Medical News*

The findings of a new, international study of 6,685 mothers and their newborns may explain why certain infant and child health problems frequently have been seen in the offspring of mothers who smoked during pregnancy, Kendall Morgan, Ph.D., wrote in the National Institutes of Health Director's Blog.

The study, published in the American Journal of Human Genetics, "found significant differences between the epigenetic patterns of babies born to women who smoked during pregnancy and those born to nonsmokers, with many of the differ-

ences affecting genes known to play key roles in the development of the lungs, face, and nervous system," Dr. Morgan wrote in the April 12 blog entry.

The new research renders more statistical power to evidence of the epigenetic effects of maternal smoking on fetuses that was found in smaller studies, Dr. Morgan wrote. In the infants of women who smoked every day during pregnancy, the researchers spotted more than 6,000 places where chemical marks on the DNA differed from those of babies born to mothers who did not smoke during pregnancy.

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## VIEW ON THE NEWS

**Dr. Vera A. De Palo, FCCP, comments:** We have long known the consequences

of cigarette smoking in individuals who continue to smoke over time regardless of the age that smoking begins. These comments and the studies cited bring focus to the effect smoking has on our genetic code and development.



# CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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# Reintubation risk reduced

NIV, high-flow from page 1

and his colleagues (JAMA. 2016 Apr 5;315[13]:1345-53).

The second study included adult patients who had received mechanical ventilation for more than 12 hours and who met criteria for being considered at low risk for reintubation. Patients were administered either high-flow oxygen therapy through nasal cannula immediately after extubation or continuous conventional oxygen therapy through nasal cannula or nonrebreather facemask; the patients were observed for 72 hours. High-flow therapy has been shown to improve oxygenation and survival in clinical studies of critically ill patients in the acute phase of respiratory failure. “[A study by S.M. Maggiore and his colleagues (Am J Respir Crit Care Med. 2014;190(3):282-8)] suggested that high-flow therapy after planned extubation decreased the reintubation rate in a general population of critical patients, but the benefits might be mainly attributable to improvements in high-risk patients,” said Dr. Gonzalo Hernandez, of the Hospital Virgen de la Salud, Toledo, Spain, and his colleagues (JAMA. 2016 Apr 5;315[13]:1354-61).

In the first study, 148 patients received NIV and 145 patients received standard oxygen therapy only. NIV was administered through a facemask connected to an ICU- or a NIV-dedicated ventilator, using either a heated humidifier or heat and moisture exchanger to warm and humidify inspired gases. Patients were encouraged to use NIV for 6 hours during the first 24 hours of the study and received standard oxygen therapy at a rate of up to 15 L/minute to maintain an arterial oxygen saturation estimate (SpO<sub>2</sub>) of at least 94% in between NIV sessions. NIV was started at an inspiratory positive airway pressure of 5 cm H<sub>2</sub>O, increasing to a maximum inspiratory pressure of 15 cm H<sub>2</sub>O, aiming to achieve an expi-

ratory tidal volume between 6 and 8 mL/kg of predicted body weight and a respiratory rate lower than 25/min. The patients in this study’s control group only received the standard oxygen therapy.

In the other study, 263 patients received conventional therapy, with the oxygen flow having been adjusted to maintain an arterial oxygen saturation estimate of greater than 92%. This study’s other 264 patients received high-flow oxygen therapy, with the flow having been initially set at 10 L/min and titrated upward in 5-L/min steps until patients experienced discomfort. The high-flow therapy was stopped after 24 hours and was followed by conventional oxygen therapy, when needed.

The primary outcome measure in the study involving NIV was cause for reintubation within 7 days of randomization.

Secondary outcome measures included gas exchange, healthcare-associated infection rate within 30 days, number of ventilator-free days between days 1 and 30, antibiotic use duration, ICU and in-hospital length of stay, and 30- and 90-day mortality.

Reintubation occurred in 49 patients in the NIV group and 66 patients in the standard oxygen therapy group, a significant difference ( $P = .03$ ). Among the reintubated patients, those who had received NIV spent less time under invasive mechanical ventilation as did the patients given standard oxygen therapy. The interquartile ranges of days of invasive mechanical ventilation were 0-3 for patients in the NIV group and 0-5 for patients in the standard oxygen therapy group ( $P = .05$ ). At 30 days, NIV was associated with significantly more ventilator-free days than standard oxygen therapy (25.4 vs. 23.2;  $P = .04$ ). At 90 days, 22 patients in the NIV group and 31 patients in the standard oxygen therapy group had died ( $P = .15$ ).

Continued from previous page

severity in the year preceding trial entry, a predicted FVC of 50% or more, and a 6MWD of 150 meters or more. Among the patients receiving antacid therapy at baseline, 88% used proton-pump inhibitors, 8% used H<sub>2</sub> blockers and 4% used proton-pump inhibitors and H<sub>2</sub> blockers. Of the 291 patients receiving antacid therapy, 38 stopped after baseline; of the 333 not receiving

antacid therapy, 83 started receiving the therapy after baseline.

Dr. Kreuter disclosed ties with Boehringer Ingelheim and InterMune/Roche. Two coauthors disclosed ties with F. Hoffmann-La Roche, which funded the study: Derek Weycker, Ph.D., reported receiving funding from the company, and Dr. Klaus-Uwe Kirchgaessler is an employee.

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“Recent high-impact trials have demonstrated the benefits in nonsurgical hypoxemic respiratory failure or equivalence of high-flow nasal cannula compared with NIV in patients after cardiothoracic surgery with moderate to severe hypoxemia. Future studies comparing use of high-flow oxygen cannula vs standard oxygen therapy and NIV for patients after abdominal surgery as preventive (prophylactic) or curative applications are needed,” according to Dr. Jaber and his colleagues.

The primary outcome measure for the study of patients receiving high-flow oxygen therapy was reintubation within 72 hours after extubation; this occurred in fewer patients in the high-flow oxygen group than in the conventional therapy group (13 or 4.9% vs. 32 or 12.2%). This statistically significant difference was mainly attributable to a lower incidence of respiratory-related reintubation in the high-flow group, compared with the conventional therapy group (1.5% vs. 8.7%), said Dr. Hernandez and his colleagues.

Secondary outcome measures included postextubation respiratory failure, respiratory infection, sepsis, multiorgan failure, ICU and hospital length of stay and mortality, time to reintubation, and adverse effects. Postintubation respiratory failure was less common in the high-flow therapy group than in the conventional therapy group (22 patients or 8.3% vs. 38 or 14.4%). Differences between the two groups in other secondary outcomes were not statistically significant.

“The main finding of this study was that high-flow oxygen signifi-



PHOTO:ISTOCK/THINKSTOCK

cantly reduced the reintubation rate in critically ill patients at low risk for extubation failure ... High-flow therapy improves oxygenation, and the lower rate of reintubation secondary to hypoxia in the high-flow group corroborates this finding. High-flow oxygen also seems to reduce other causes of respiratory failure such as increased work of breathing and respiratory muscle fatigue, which are frequently associated with reintubation secondary to hypoxia. Another way in which high-flow therapy improves extubation outcome is by conditioning the inspired gas,” said Dr. Hernandez and his colleagues.

No adverse events were reported in either study.

Dr. Hernandez and his colleagues reported no conflicts of interest. Dr. Jaber and his colleagues disclosed no potential conflicts of interest with their study’s sponsors, Montpellier (France) University Hospital and the APARD Foundation.

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## VIEW ON THE NEWS

**Dr. Eric Gartman, FCCP, comments:** These two studies augment a growing body of literature supporting the use of adjunctive therapies immediately following extubation to prevent reintubation for respiratory failure.

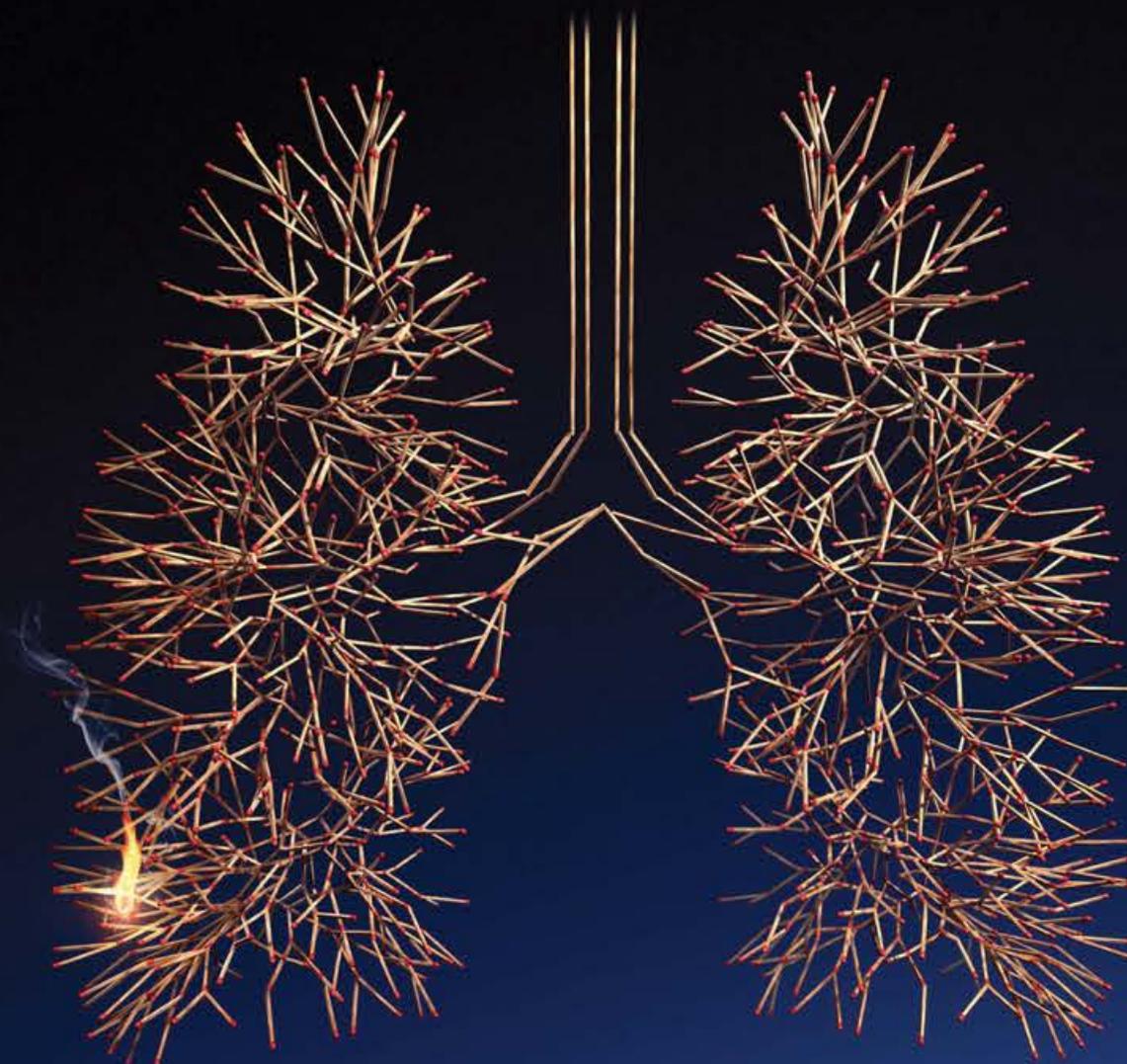
It has been known for several years that the use of noninvasive ventilation (NIV) immediately after extubation in COPD patients prevents reintubation rates, and these new data demonstrate efficacy in an expanded population. Further, the use of high-flow humidified oxygen therapy in acute respiratory failure has been shown to prevent progression to initial intubation, and now these data expand poten-

tial use to prevent reintubation, as well.

While not studied, if high-flow oxygen therapy is found to be equivalent to NIV to prevent reintubation (similar to the previously-published prevention of intubation studies) that would be clinically important since there is a significant difference in tolerance to these two therapies. Across these trials, the very important point to remember is that these therapies were found to be effective if put on directly after extubation, and one cannot wait to apply them at the point where the patient shows signs of respiratory decline.

For reducing the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

## BEFORE ONE EXACERBATION CAN LEAD TO ANOTHER,<sup>1</sup> **ADD DALIRESP**



### INDICATION AND USAGE

DALIRESP® (roflumilast) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

### IMPORTANT SAFETY INFORMATION

#### Contraindications

DALIRESP® (roflumilast) is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

#### Warnings and Precautions

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using

DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP

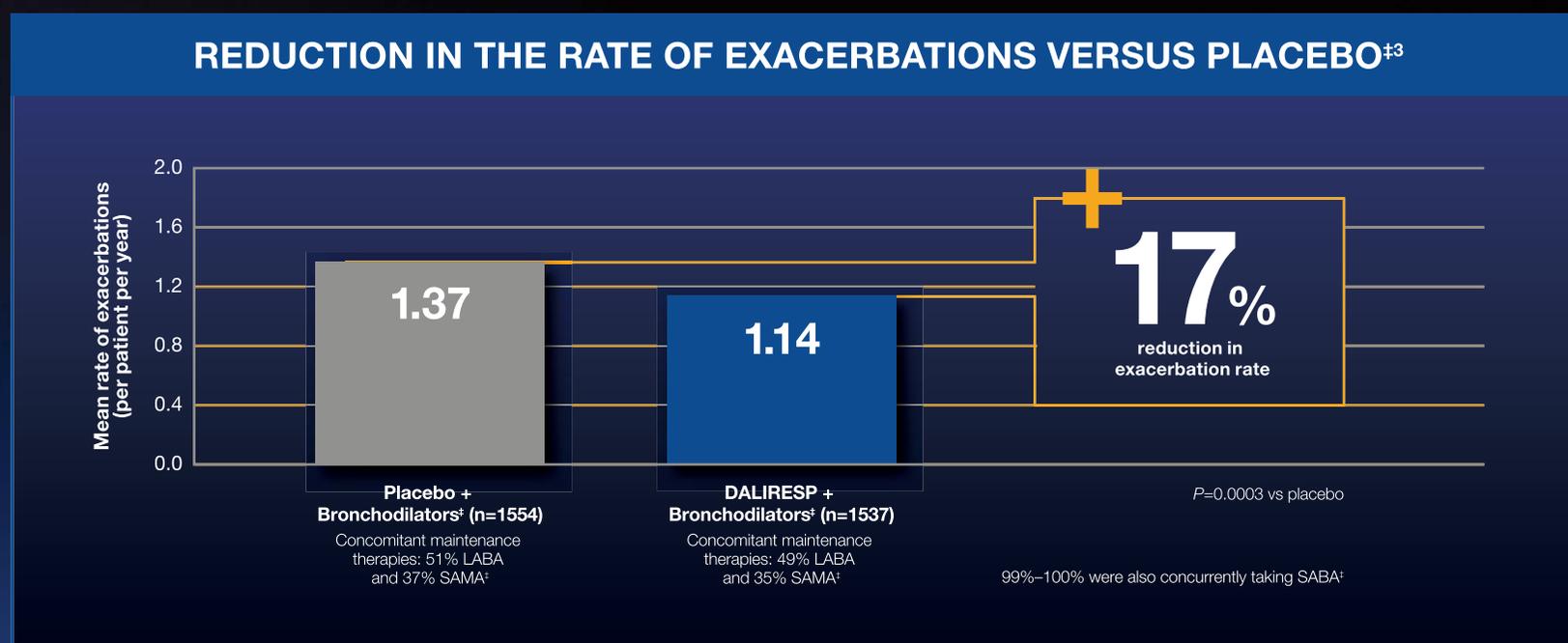
- Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate

The first and only once-daily tablet to provide enhanced protection against COPD exacerbations\*<sup>2</sup>

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm

In the two 1-year pivotal studies:

Significantly reduced the rate of moderate or severe exacerbations<sup>†</sup> on top of current bronchodilator therapy<sup>‡3</sup>



weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost

- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP

#### Adverse Reactions

In clinical trials, the most common adverse reactions ( $\geq 2\%$  and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see Brief Summary on the following page.

\*In the two 1-year pivotal studies, DALIRESP was added to bronchodilators, including long-acting  $\beta_2$  agonists (LABA), or short-acting muscarinic antagonists (SAMA), and short-acting  $\beta_2$  agonists (SABA).

<sup>†</sup>Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids, and severe exacerbations were defined as those resulting in hospitalization or death.

<sup>‡</sup>Patients were allowed to be on LABA or SAMA at stable doses. SABA was allowed for rescue use. In the pooled analysis, the use of concomitant bronchodilators in the placebo group vs DALIRESP group were: LABA (51% vs 49%), SAMA (37% vs 35%), and SABA (99% vs 100%).

**Study design:** A pooled analysis of two identical, 1-year, double-blind, placebo-controlled studies of 3091 patients with severe COPD associated with chronic bronchitis and a history of exacerbations compared DALIRESP (n=1537) and placebo (n=1554). Subjects were current or ex-smokers with a smoking history of >20 pack-years, aged >40 with a clinical diagnosis of COPD with chronic cough and sputum production. The study included a 4-week run-in period followed by a 1-year treatment period. Subjects could use SABAs as needed and could continue treatment with LABAs or SAMAs at stable doses. The studies were designed to assess the rate of moderate or severe COPD exacerbations and the change from baseline in pre-bronchodilator FEV<sub>1</sub>.

**References:** 1. Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;179:369-374. 2. DALIRESP Prescribing Information. Wilmington, DE; AstraZeneca Pharmaceuticals LP; November 2015. 3. Calverley PMA, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 Study Groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374:685-694.



## DALIRESP® (roflumilast) tablets

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

### INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

#### Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

### DOSAGE AND ADMINISTRATION

The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

### CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following condition:

Moderate to severe liver impairment (Child-Pugh B or C) [see *Clinical Pharmacology (12.3) and Use in Specific Populations (8.6) in the full Prescribing Information*].

### WARNINGS AND PRECAUTIONS

#### Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

#### Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [see *Adverse Reactions (6.1) in the full Prescribing Information*]. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo. Cases of suicidal ideation and behavior, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

#### Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [see *Adverse Reactions (6.1) in the full Prescribing Information*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

#### Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [see *Drugs that Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

### ADVERSE REACTIONS

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

- Psychiatric Events Including Suicidality [see *Warnings and Precautions (5.2) in the full Prescribing Information*]
- Weight Decrease [see *Warnings and Precautions (5.3) in the full Prescribing Information*]

#### Adverse Reactions in Clinical Studies

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

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials [see *Clinical Studies (14.1)*]. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV<sub>1</sub>) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

**Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo**

Adverse Reactions (Preferred Term)	Treatment	
	DALIRESP (N=4438)	Placebo (N=4192)
	n (%)	n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting

Infections and infestations - rhinitis, sinusitis, urinary tract infection

Musculoskeletal and connective tissue disorders - muscle spasms

Nervous system disorders - tremor

Psychiatric disorders - anxiety, depression

### Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of DALIRESP received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to DALIRESP. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to DALIRESP exposure: hypersensitivity reactions (including angioedema, urticaria and rash), gynecomastia.

### DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

#### Drugs that Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended [see *Drug Interactions (5.4) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

#### Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

#### Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

### USE IN SPECIFIC POPULATIONS

#### Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m<sup>2</sup> basis at maternal doses >2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m<sup>2</sup> basis at maternal doses ≥0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m<sup>2</sup> basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg<sup>2</sup> basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m<sup>2</sup> basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

#### Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m<sup>2</sup> basis at a maternal dose of >2 mg/kg/day).

#### Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

#### Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

#### Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were >65 years of age and 471 were >75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

#### Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C<sub>max</sub> of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) [see *Contraindications (4) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

#### Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C<sub>max</sub> were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

### OVERDOSAGE

#### Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

#### Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

### PATIENT COUNSELING INFORMATION

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

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## COPD screens nixed for the asymptomatic

USPSTF from page 1

programs. One trial showed a statistically significant increase in smoking cessation rates between participants who received explanations of their spirometry results using 'lung age' and those who did not. The other four trials did not report any significant differences in smoking abstinence rates."

The recommendations are based on a systematic review of evidence that was commissioned by the USPSTF and published in the same issue of JAMA. The reviewers set out to determine the accuracy of screening questionnaires and office-based screening pulmonary function testing and the efficacy and harms of treatment of screen-detected COPD. After reviewing 33 studies that met inclusion criteria, five experts led by Dr. Janelle M. Guirguis-Blake found "no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations," they wrote (JAMA. 2016 Apr; 315[13]:1378-93). "Indirect evidence suggests that the CDQ [COPD Diagnostic Questionnaire] has moderate overall performance for COPD detection. Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest."

The USPSTF last published an update on COPD screening in 2008. That report recommended

against screening for COPD with spirometry in asymptomatic adults, a Grade D recommendation based on the conclusion that screening for COPD had no net benefit and large associated costs.

According to the current recommendations, an estimated 14% of U.S. adults aged 40-79 years have COPD, and it is the third leading cause of death in the U.S. Although postbronchodilator spirometry is required to make a definitive diagnosis, "prescreening questionnaires can elicit current symptoms and previous exposures to harmful particles or gases," Dr. Siu and his fellow task force members wrote.

They acknowledged limitations of the recommendations, including the fact that many of the reviewed studies did not report results separately by current versus former smokers. "Future studies that stratify risk by smoking status could help identify different risk groups that may benefit from screening," they wrote "In addition, trials are needed that assess the effects of screening among current and previous smokers in primary care on long-term health outcomes. Long-term trials of treatment of COPD in screen-detected patients are also needed. Better treatment options for COPD and long-term epidemiological studies of the natural history and heterogeneity of COPD progression could also help identify patients who are at greatest risk for clinical deterioration."

The systematic literature review was funded by

### VIEW ON THE NEWS

**Dr. John Studdard, President-Designate, American College of Chest Physicians, comments:**

The US Preventive Services Task Force recommendation not to routinely screen adults without respiratory symptoms should not be confused with screening individuals with qualifying risk factors or symptoms such as a history of smoking, long-term exposure to air pollutants, cough, feeling out of breath, and wheezing. We know COPD is woefully underdiagnosed, and those undiagnosed could have better quality of life if this diagnosis is made. Clinicians should consider respiratory symptoms as a potential symptom of COPD and not simply the patient aging or being physically out of shape. Spirometry testing, a simple, noninvasive test to determine how the lungs are functioning, should be performed on patients after considering personal history and evaluation of symptoms.



the Agency for Healthcare Research and Quality under a contract to support the USPSTF. The authors of the recommendation statement reported having no financial disclosures.

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## Compelling case for novel oral anticoagulants in VTE

BY BRUCE JANCIN  
Frontline Medical News

SNOWMASS, COLO. – All four Food and Drug Administration–approved novel oral anticoagulants offer impressive safety advantages over the traditional strategy of low-molecular-weight heparin bridging to warfarin for treatment of acute venous thromboembolism, Dr. Patrick T. O’Gara observed at the Annual Cardiovascular Conference at Snowmass.

He highlighted a European analysis of six phase III clinical trials totaling more than 27,000 patients with venous thromboembolism (VTE) in which dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), or edoxaban (Savaysa) was compared to the traditional strategy of unfractionated or low-molecular-weight heparin (LMWH) bridging to warfarin or another vitamin K antagonist. All four NOACs proved statistically noninferior to the traditional strategy in terms of efficacy as defined by prevention of recurrent VTE. Efficacy of NOACs and warfarin was similar regardless of body weight, chronic kidney disease, age, cancer, and pulmonary embolism versus deep venous thrombosis.

In terms of safety, it was no contest: The NOACs were collectively associated with a 39% lower risk of major bleeding, a 64% lower risk of fatal bleeding, and a 63% reduction in intracranial bleeding compared to LMWH/warfarin (Blood 2014 Sep 18;124[12]:1968-75).



**Fast-acting antidotes to NOACs have emerged, further strengthening their case for routine use.**

DR. O’GARA

"This is a big-ticket winner for the novel oral anticoagulants in the longer-term management of patients who have venous thromboembolic disease – not inferior to a strategy of low-molecular-weight heparin bridging to warfarin and much better with respect to serious consequences of a safety nature," said Dr. O’Gara, professor of medicine at Harvard Medical School and director of clinical cardiology at Brigham and Women’s Hospital, Boston.

The pivotal trials for NOACs in

VTE were generally structured statistically as noninferiority trials, with one exception: edoxaban has been shown to be superior to warfarin in a prespecified subgroup with submassive pulmonary embolism.

Further strengthening the case for routine use of NOACs in treating acute VTE is the emergence of fast-acting antidotes to the drugs in the event a patient develops a bleeding complication. Idarucizumab (Praxbind) received FDA approval last October as a reversal agent for dabigatran. Many experts think andexanet alpha will likely receive regulatory approval later this year as a universal antidote to all the factor Xa inhibitors, he noted.

It’s estimated that 70% of patients with pulmonary embolism can be classified as low risk and thus eligible for consideration for early hospital discharge and home treatment, provided their social situation is suitable. Pulmonary embolism patients are categorized as low risk if they are hemodynamically stable, don’t require supplemental oxygen, don’t show right ventricular dilatation on CT imaging in the emergency department, and lack serum biomarker evidence of right ventricular strain or injury.

In making decisions about outpatient therapy for VTE, a point worth considering is that two NOACs, rivaroxaban and apixaban, possess the practical advantage of being single-agent therapy. That is, they don’t require a heparin bridge prior to their introduction, as established in the EINSTEIN trial for rivaroxaban and in the AMPLIFY study for apixaban. However, a loading dose is necessary. Rivaroxaban is given at 15 mg b.i.d. for 3 weeks before dropping down to 20 mg once daily. Apixaban has a loading dose of 10 mg b.i.d. for the first 7 days followed by 5 mg b.i.d. thereafter.

"You’ll note that you give a higher loading dose for these particular agents for events that occur on the venous side of the circulation compared with the management of patients who have nonvalvular atrial fibrillation," Dr. O’Gara said.

In contrast, both dabigatran and edoxaban require either unfractionated or LMWH as bridge before switching to oral therapy.

Dr. O’Gara reported having no financial conflicts of interest regarding his presentation.

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# Recent active asthma linked to AAA rupture in aged

BY JENNIE SMITH  
Frontline Medical News

Patients aged 50 and older with recent active asthma and an abdominal aortic aneurysm are at elevated risk of aneurysm rupture, according to new research.

A common inflammatory pathway between asthma and AAA, first observed nearly a decade ago in mice, is thought to be responsible.

The new findings, published online in *Arteriosclerosis, Thrombosis, and Vascular Biology* (Arterioscler Thromb Vasc Biol. 2016. doi: 10.1161/ATVBAHA.115.306497) support the association in humans.

The findings have clear clinical implications for older patients with a recent asthma diagnosis. Such patients, particularly older men, “should be checked for signs” of abdominal aortic aneurysm, lead study author Guo-Ping Shi, D.Sc., of Brigham and Women’s Hospital and Harvard Med-

ical School, Boston, said in a news release accompanying the findings.

For their research, Dr. Shi, along with colleagues at Zhengzhou (China) University, used data from a large Danish population-based cohort of nearly 16,000 patients, 81% of them men, diagnosed with AAA between 1996 and 2012. About 4,500 of these patients later had a ruptured AAA. The researchers also looked at data from a comparison cohort of patients with and without AAA from a slightly larger population-based vascular screening trial of men in Denmark.

Of the 514 patients given an in-hospital diagnosis of asthma within the previous year, 146 had a hospital admission for a ruptured AAA rupture. Both before and after adjustment for AAA comorbidities, these patients had a significantly higher risk of a ruptured AAA than other patients (adjusted odds ratio = 1.51-2.06). A higher risk of a ruptured AAA also was seen for patients filling prescriptions for bronchodilators within the previous 3 months (adjusted odds ratio = 1.10-1.31), and for patients prescribed anti-asthma drugs (adjusted odds ratio = 1.09-1.48).

A hospital diagnosis of asthma or a recently filled prescription of an anti-asthmatic drug was associated with an increased risk of admission with a ruptured AAA compared with admission with an intact AAA, both before and after adjusting for AAA comorbidities and relevant medications, the researchers wrote in their analysis.

Moreover, “an asthma diagnosis or the use of bronchodilators or other anti-asthmatic drug prescriptions closer to the date of admission with AAA correlated directly with a higher risk of aortic rupture. The results remained robust after adjusting for a wide range of relevant possible confounders,” the researchers wrote.



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After adjusting for AAA comorbidities, the odds ratio was 1.51-2.06.

## VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: This is a very intriguing study resulting from the analysis of two large population cohorts examining the potential association between active asthma and AAA risk. From prior animal studies, it has been suggested that the link may arise from a common inflammatory/immune pathway. If this association is real, it would certainly lead clinicians to



be more vigilant and proactive in this population of patients. One caution in this method of study of using large datasets is that it is reliant on a code for a diagnosis that is not rigorously defined (i.e. could be coded as asthma, but patient actually has COPD or something else) and that the “asthma” treatments that were used to define the population could be used for another condition.

In the cohort of patients from the vascular screening study, which included age-matched controls without AAA, recent anti-asthmatic medication use was associated with

**A hospital diagnosis of asthma or a recently filled prescription of an anti-asthmatic drug is associated with an increased risk of admission with a ruptured AAA compared with admission with an intact AAA, both before and after adjusting for AAA comorbidities and relevant medications.**

a significantly elevated risk of having an AAA. This association with the presence of AAA was seen before and after adjustment for smoking (odds ratio = 1.45) and for other risk factors (odds ratio = 1.46).

Dr. Shi and colleagues noted that there was insufficient information on cigarette smoking, a known risk factor for AAA and AAA rupture, in the cohort with established AAAs

and so there is the possibility of confounding in that aspect of the study. However, the second all-male cohort did have extensive data on smoking. Even after adjustment for smoking, the risk of AAA remained 45% higher in patients with asthma as compared with patients without asthma.

The researchers hypothesized that an inflammatory response characterized by elevated immunoglobulin E may be the link between AAA pathogenesis and asthma, and that other allergic inflammatory diseases, including atopic dermatitis, allergic rhinitis, and some ocular allergic diseases, could potentially carry risks for AAA formation and rupture. Dr. Shi and colleagues previously investigated the IgE and aneurysm link in animal studies.

“The results have implications for the development of much needed advances in the prevention, screening criteria, and treatment of AAA, common conditions for which we currently lack sufficiently effective approaches,” the investigators wrote.

The Chinese, Danish, and U.S. governments sponsored the study. The investigators disclosed no conflicts of interest.

# Sublingual immunotherapy delayed asthma exacerbation

BY MARY ANN MOON  
Frontline Medical News

Immunotherapy using sublingual tablets containing house dust mite allergen extended the interval until patients developed a moderate asthma exacerbation in a manufacturer-sponsored clinical trial reported online April 26 in *JAMA*.

However, patients’ scores on both the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire showed no difference between active treatment and placebo. And 25%-27% of the study participants dropped out of the

study, usually citing asthma exacerbations, adverse events, or “withdrawal of consent.” Further studies are needed to assess long-term efficacy and safety, said Dr. J. Christian Virchow of the department of pulmonology/intensive care medicine, University of Rostock (Germany), and his associates.

The trial, involving 834 adults with asthma related to house dust mite allergy that was not well controlled by inhaled corticosteroids and short-acting beta-agonists, was performed at 109 sites in 13 European countries during a 2-year

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period. These participants were randomly assigned to receive add-on daily sublingual tablets containing low-dose dust-mite extract (275 patients), high-dose extract (282 patients), or placebo (277 patients) for 7-12 months. During the final 6 months of the intervention, corticosteroids were reduced by half for 3 months and then withdrawn for 3 months.

The primary efficacy outcome (time to the first asthma exacerbation) was extended by both doses of active drug, compared with placebo, with hazard ratios of 0.69 for the lower dose and 0.66 for the higher dose, the investigators said (JAMA. 2016 Apr 26;315[16]:1715-25).

Adverse events were significantly more frequent with active treat-

### Time to the first asthma exacerbation was extended by both doses of active drug, compared with placebo, with hazard ratios of 0.69 for the lower dose and 0.66 for the higher dose.

ment, affecting 39% of patients receiving the lower dose and 46% of those receiving the higher dose

of active immunotherapy, compared with only 17% of patients receiving placebo. However, this study was

not adequately powered to compare adverse events across groups, Dr. Virchow and his associates noted.

The most frequently reported adverse events were oral pruritus, mouth edema, and throat irritation, which developed within a median of 1-2 minutes of taking the first

Continued on following page

#### VIEW ON THE NEWS

## Asthma control, QOL no different

Sublingual immunotherapy appears to be somewhat less effective than subcutaneous immunotherapy, but it offers several advantages. It doesn't require injections, can be self-administered, doesn't require dose escalations, and carries a much lower risk of anaphylaxis. However, in this study there were no significant differences in patients' responses to questionnaires regarding either asthma control or quality of life.

The main disadvantage is that sublingual immunotherapy requires adherence to daily dosing, and research has consistently shown low rates of long-term adherence. In one study, 55%-82% of patients failed to complete the recommended course of sublingual immunotherapy. In another, only 44% of patients renewed their prescriptions after 1 year of treatment, only 28% did so after 2 years, and only 13% did so after 3 years.

Dr. Robert A. Wood is in the division of allergy and immunology, department of pediatrics, at Johns Hopkins University, Baltimore. He reported ties to DBV Technologies, the Immune Tolerance Network, Stallergenes, Sanofi, and UpToDate. Dr. Wood made these remarks in an editorial accompanying Dr. Virchow's report (JAMA. 2016 Apr 26;315:1711-2).

## Of all the things you recommend to protect your patients aged 65+



GET VACCINATED  
AGAINST PNEUMOCOCCAL  
PNEUMONIA

## HERE'S ONE YOU CAN GET DONE TODAY

Make vaccination a priority.

Help protect your appropriate patients with Prevnar 13®.

- Pneumococcal pneumonia can have serious consequences and may lead to hospitalization<sup>1</sup>
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- Prevnar 13® is covered by the Medicare Part B FFS benefit for adults aged 65+ with \$0 in out-of-pocket costs

Learn more about Prevnar 13® and the information above at [www.Prevnar13info.com](http://www.Prevnar13info.com)

ACIP=Advisory Committee on Immunization Practices; CDC=Centers for Disease Control and Prevention; FFS=fee-for-service; IPD=invasive pneumococcal disease.

#### INDICATION

- In adults 50 years of age and older, Prevnar 13® is indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

#### Limitations of Use and Effectiveness

- Prevnar 13® will only help protect against *S pneumoniae* serotypes in the vaccine

#### IMPORTANT SAFETY INFORMATION

- Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid-containing vaccine is a contraindication
- Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response
- In adults, antibody responses to Prevnar 13® were diminished when given with inactivated trivalent influenza vaccine
- In adults, the commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle or joint pain, decreased appetite, chills, or rash

#### Please see Brief Summary of Prescribing Information on adjacent page(s).

**References:** 1. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med.* 2013;369(2):155-163. 2. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2014;63(37):822-825. 3. Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med.* 2015;372(12):1114-1125.

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**Prevnar 13®**  
Pneumococcal 13-valent Conjugate Vaccine  
(Diphtheria CRM<sub>197</sub> Protein)

Continued from previous page

dose on day 1 and persisted for a median of 4-23 days. There were 32 serious adverse events, including erosive esophagitis, hepatocellular injury, arthralgia, laryngeal edema, and asthma.

This trial was limited in that treat-

ment duration was much shorter than that for a standard course of immunotherapy, which is often 3 years. This prevents drawing conclusions regarding the sustained effect of the treatment. "Furthermore, because the ultimate aim of allergen immunotherapy is disease modification beyond the duration of treatment, a

follow-up after the end of treatment would have been relevant," the investigators said.

This study was sponsored by the Danish pharmaceutical company ALK. Dr. Virchow reported ties to 31 industry sources; his associates also reported ties to numerous industry sources.

#### BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION



This brief summary does not include all of the information needed to use Pneumovax 23 safely and effectively. Before prescribing, please consult the full Prescribing Information for Pneumovax 23.

#### DOSAGE FORMS AND STRENGTHS

Pneumovax 23 is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

#### CONTRAINDICATIONS

Severe allergic reaction (eg, anaphylaxis) to any component of Pneumovax 23 or any diphtheria toxoid-containing vaccine.

#### WARNINGS AND PRECAUTIONS

##### Management of Allergic Reactions

Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Pneumovax 23.

##### Altered Immunocompetence

Data on the safety and effectiveness of Pneumovax 23 when administered to immunocompromised individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced antibody response to active immunization due to impaired immune responsiveness.

##### Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Pneumovax 23, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

#### ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of Pneumovax 23 could reveal adverse reactions not observed in clinical trials.

##### Clinical Trials Experience With Pneumovax 23 in Infants and Toddlers

The safety of Pneumovax 23 was evaluated in 13 clinical trials in which 4729 infants and toddlers received at least 1 dose of Pneumovax 23 and 2760 infants and toddlers received at least 1 dose of Pneumovax 23 active control. Overall, the safety data show a similar proportion of Pneumovax 23 and Pneumovax 23 active control subjects reporting serious adverse events. Among US study subjects, a similar proportion of Pneumovax 23 and Pneumovax 23 active control recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

##### Serious Adverse Events in All Infant and Toddler Clinical Studies

Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Pneumovax 23 recipients and 7.2% among Pneumovax 23 active control recipients. Serious adverse events observed during different study periods for Pneumovax 23 and Pneumovax 23 active control, respectively, were: 1) 3.7% and 3.5% from dose 1 to the bleed approximately 1 month after the infant series; 2) 3.6% and 2.7% from the bleed after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the bleed approximately 1 month after the toddler dose; and 4) 2.5% and 2.8% during the 6-month follow-up period after the last dose.

The most commonly reported serious adverse events were in the "Infections and infestations" system organ class, including bronchiolitis (0.9%, 1.1%), gastroenteritis (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Pneumovax 23 and Pneumovax 23 active control, respectively.

There were 3 (0.063%) deaths among Pneumovax 23 recipients and 1 (0.036%) death among Pneumovax 23 active control recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age-specific background rates of SIDS from the year 2000.

Among 6839 subjects who received at least 1 dose of Pneumovax 23 in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4204 subjects who received at least 1 dose of Pneumovax 23 in clinical trials conducted globally, there were 3 hypotonic-hyporesponsive episode adverse reactions reported (0.071%). All 4 events occurred in a single clinical trial in Brazil in which subjects received whole cell pertussis vaccine at the same time as Pneumovax 23 or Pneumovax 23 active control.

##### Solicited Adverse Reactions in the 3 US Infant and Toddler Studies

A total of 1907 subjects received at least 1 dose of Pneumovax 23 and 701 subjects received at least 1 dose of Pneumovax 23 active control in the 3 US studies.

Solicited adverse reactions that occurred within 7 days following each dose of Pneumovax 23 or Pneumovax 23 active control administered to US infants and toddlers were: in infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%).

##### Unsolicited Adverse Reactions in the 3 US Infant and Toddler Safety Studies

The following were determined to be adverse drug reactions based on experience with Pneumovax 23 in clinical trials: reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash; and reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

##### Clinical Trials Experience With Pneumovax 23 in Adults Aged ≥50 Years

The safety of Pneumovax 23 was assessed in 7 clinical studies (Studies 6-12) conducted in the US and Europe, which included 90,694 adults (47,907 received Pneumovax 23) ranging in age from 50 through 101 years.

The 47,907 Pneumovax 23 recipients included 2616 adults who were aged 50 through 64 years and 45,291 adults aged 65 years and older. Of the 47,907 Pneumovax 23 recipients, 45,991 adults had not previously received PPSV23 ("PPSV23 unvaccinated") and 1916 adults were previously

vaccinated ("PPSV23 previously vaccinated") with PPSV23 at least 3 years prior to enrollment.

##### Serious Adverse Events in Adult Clinical Studies

Across the 6 safety and immunogenicity studies, serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5055 subjects vaccinated with Pneumovax 23 and in 0.4%-1.7% of 1124 subjects vaccinated after an initial study dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23). From 1 month to 6 months after an initial study dose, serious adverse events were reported in 1.2%-5.8% of subjects vaccinated during the studies with Pneumovax 23 and in 2.4%-5.5% of subjects vaccinated with PPSV23. One case of erythema multiforme occurred 34 days after receipt of a second dose of Pneumovax 23.

Twelve of 5667 (0.21%) Pneumovax 23 recipients and 4 of 1391 (0.29%) PPSV23 recipients died. Deaths occurred between day 3 and day 309 after study vaccination with Pneumovax 23 or PPSV23. Two of 12 deaths occurred within 30 days of vaccination with Pneumovax 23 and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving Pneumovax 23 administered with trivalent inactivated influenza vaccine (TIV) and the other death was due to peritonitis 20 days after receiving Pneumovax 23. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Pneumovax 23 were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1), and septic shock (1).

In an efficacy study of subjects 65 years of age and older, serious adverse events within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Pneumovax 23 recipients (352 events) and in 314 of 42,225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1006 (7%) Pneumovax 23 vaccinated subjects (90 events) and 60 of 1005 (6%) placebo vaccinated subjects (69 events) reported serious adverse events.

During the follow-up period (average of 4 years) for case accumulation there were 3006 deaths (7.1%) in the Pneumovax 23 group and 3005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Pneumovax 23 group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Pneumovax 23 group and 144 deaths (0.3%) in the placebo group within 29 days - 6 months following vaccination. These data do not provide evidence for a causal relationship between deaths and vaccination with Pneumovax 23.

##### Solicited Adverse Reactions in Adult Clinical Studies

In adults aged 50 years and older, the commonly reported solicited adverse reactions were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), chills (>5%), or rash (>5%).

##### Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Pneumovax 23 and TIV (Fluarix)

The safety of concomitant administration of Pneumovax 23 with TIV was assessed in 2 studies in PPSV23 unvaccinated adults aged 50 through 59 years and aged ≥65 years.

Frequencies of local reactions within 14 days post-vaccination in adults aged 50 through 59 years and in adults aged ≥65 years were similar after Pneumovax 23 was administered with TIV compared to Pneumovax 23 administered alone, with the exception of mild redness at the injection site, which was increased when Pneumovax 23 was administered concomitantly with TIV.

An increase in some solicited systemic reactions within 14 days post-vaccination was noted when Pneumovax 23 was administered concomitantly with TIV compared with TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with Pneumovax 23 given alone (fatigue, headache, chills, decreased appetite, and joint pain).

##### Clinical Trials Experience With Pneumovax 23 in Infants and Toddlers

The safety experience with Pneumovax 23 is relevant to Pneumovax 23 because the 2 vaccines share common components.

Generally, the adverse reactions reported in clinical trials with Pneumovax 23 were also reported in clinical trials with Pneumovax 23 active control.

Overall, the safety of Pneumovax 23 was evaluated in a total of 5 clinical studies in the United States in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age.

Adverse events reported in clinical trials with Pneumovax 23 that occurred within 3 days of vaccination in infants and toddlers and resulted in emergency room visits or hospitalizations, but were not presented in Section 6.1 as adverse reactions for Pneumovax 23, are listed below:

Bronchiolitis, UTI, acute gastroenteritis, asthma, aspiration, breath holding, influenza, inguinal hernia repair, viral syndrome, URI, croup, thrush, wheezing, choking, conjunctivitis, pharyngitis, colic, colitis, congestive heart failure, roseola, and sepsis.

##### Post-marketing Experience With Pneumovax 23 in Infants and Toddlers

The following adverse events have been reported through passive surveillance since market introduction of Pneumovax 23 and, therefore, are considered adverse events for Pneumovax 23 as well. Because these events 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 the vaccine.

**Administration site conditions:** Injection site dermatitis, injection site pruritus, injection site urticaria

**Blood and lymphatic system disorders:** Lymphadenopathy localized to the region of the injection site

**Immune system disorders:** Anaphylactic/anaphylactoid reaction including shock

**Skin and subcutaneous tissue disorders:** Angioneurotic edema, erythema multiforme

**Respiratory:** Apnea

#### DRUG INTERACTIONS

##### Concomitant Immunizations

In clinical trials with infants and toddlers, Pneumovax 23 was administered concomitantly with the following US licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first 3 doses and with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella, and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A Vaccine, Inactivated] (HepA) for dose 4.

In adults, Pneumovax 23 was administered concomitantly with US licensed Fluarix (TIV) for the 2007/2008 influenza season. There are no data on the concomitant administration of Pneumovax 23 with diphtheria toxoid-containing vaccines and other vaccines licensed for use in adults 50 years of age and older.

When Pneumovax 23 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

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Do not mix Pneumovax 23 with other vaccines/products in the same syringe.

##### Immunosuppressive Therapies

Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

##### Antipyretics

A post-marketing clinical study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Pneumovax 23. The data show that 3 doses of acetaminophen (the first dose administered at the time of each vaccination and the subsequent doses at 6 to 8 hour intervals) reduced the antibody response to some serotypes following the third dose of Pneumovax 23, compared with responses among infants who received antipyretics only as needed for treatment. Reduced antibody responses were not observed after the fourth dose of Pneumovax 23 when acetaminophen was administered prophylactically.

##### Prior Vaccination With PPSV23

Prior receipt of Pneumovax 23 (23 valent pneumococcal vaccine polyvalent, PPSV23) within 1 year results in diminished immune responses to Pneumovax 23 compared to PPSV23 naive individuals.

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

##### Pregnancy Category B

A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to Pneumovax 23. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

##### Nursing Mothers

It is not known whether this vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Pneumovax 23 is administered to a nursing woman.

##### Pediatric Use

Safety and effectiveness of Pneumovax 23 in children below the age of 6 weeks or on or after the 6th birthday have not been established.

Immune responses elicited by Pneumovax 23 among infants born prematurely have not been specifically studied.

##### Geriatric Use

Of the total number of Pneumovax 23 recipients aged 50 years and older in clinical studies (N=47,907), 94.5% (45,291 of 47,907) were 65 years and older and 30.3% (14,498 of 47,907) were 75 years and older.

##### High Risk Populations

Individuals with the diseases or conditions listed below are at increased risk of pneumococcal disease. Immunogenicity and safety data in these populations are limited.

##### Infants Born Prematurely

Immune responses elicited by Pneumovax 23 administered on a US schedule to preterm infants have not been studied. When preterm infants (<37 weeks gestational age, N=100) were administered 4 doses of Pneumovax 23 on a non-US schedule, the serotype-specific IgG antibody responses after the third and fourth dose were lower compared to responses among term infants (≥37 weeks gestational age, N=100) for some serotypes; the effectiveness of Pneumovax 23 in preterm infants cannot be established from this study.

##### Children With Sickle Cell Disease

In an open-label, single-arm, descriptive study, 2 doses of Pneumovax 23 were administered 6 months apart to children ≥6 to <18 years of age with sickle cell disease who previously received PPSV23 at least 6 months prior to enrollment. Children with a prior history of pneumococcal conjugate vaccination were excluded. For all vaccine serotypes, anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after the first dose compared to pre-vaccination (N=95-131); OPA GMTs following the first and second dose were comparable. The effectiveness of Pneumovax 23 in this specific population has not been established.

##### Adults With HIV Infection

In an open-label, single-arm, descriptive study, 3 doses of Pneumovax 23 were administered 6 months apart to HIV-infected adults ≥50 years of age (median age 55 years), with CD4 counts ≥200 cells/μL and serum HIV RNA titer <50,000 copies/mL. All subjects had been vaccinated previously with PPSV23 at least 6 months prior to enrollment. For all vaccine serotypes anti-pneumococcal OPA GMTs were higher after the first dose compared to pre-vaccination (N=94-108); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Pneumovax 23 in this specific population has not been established.

#### PATIENT COUNSELING INFORMATION

##### Potential Benefits and Risks

Prior to administration of this vaccine, the health care professional should inform the individual, parent, guardian, or other responsible adult of the following potential benefits and risks of immunization with Pneumovax 23 [see *Warnings and Precautions (5) and Adverse Reactions (6)*], the importance of completing the immunization series for their child(ren) unless contraindicated, and that any suspected adverse reactions should be reported to their healthcare professional.

Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

This product's label may have been updated. For current Prescribing Information and further product information, please visit [www.pfizerpro.com/products](http://www.pfizerpro.com/products) or call Pfizer Medical Information toll-free at 1-800-438-1985.



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United States Patent Number: 5,614,382.

# Tumor lymphocytic infiltration predicts survival

BY JENNIFER SHEPPHARD  
Frontline Medical News

**T**umor lymphocytic infiltration (TLI), categorized as intense or nonintense, was an independent prognostic indicator for survival in non-small cell lung cancer (NSCLC).

Patients with intense TLI had significantly longer overall survival (OS) and disease-free survival (DFS), compared with patients who had nonintense TLI. In the validation data set, 5-year OS for patients with intense TLI was 85% (95% confidence interval, 70-92), compared with 58% (95% CI, 54-62) for patients with nonintense TLI ( $P = .002$ ). Five-year DFS was 79% (95% CI, 65-88) for intense and 50% (95% CI, 47-54) for nonintense TLI ( $P = .001$ ).

The retrospective study evaluated data from four randomized clinical trials, separated into a discovery set of 783 patient samples and a validation set of 763 patient samples. The LACE-Bio (Lung Adjuvant Cisplatin Evaluation Biomarker) collaborative group trials examined the benefit of platinum-based adjuvant chemotherapy in NSCLC. The median follow-up for the discovery and validation sets were 4.8 and 6.0 years, respectively.



**'The results raise the question about whether lymphocytic infiltration should be considered a stratification factor in trials that test immunotherapy or immunomodulation.'**

Differences in outcomes according to TLI were significant in both discovery and validation data sets. In the discovery set, hazard ratios for OS and DFS were 0.56 (95% CI, 0.39-0.81;  $P = .002$ ) and 0.59 (95% CI, 0.42-0.83;  $P = .002$ ), respectively.

In the validation set, OS and DFS hazard ratios were 0.45 (95% CI, 0.23-0.85;  $P = .01$ ) and 0.44 (95% CI, 0.24-0.78;  $P = .005$ ), respectively. Differences in risk reductions between the two data sets may be a result of differences in trial populations.

"The results raise the question about whether lymphocytic infiltration should be considered a stratification factor in trials that test immunotherapy or immunomodulation.

"Therefore, as suggested recently for CD8 density level in NSCLC, which predicted survival independently of all other variables and within each pathologic stage, intense lymphocytic infiltration could be a good candidate marker for establishing a [tumor node metastasis] immunoscore," wrote Dr. Elisabeth Brambilla of Institut Albert Bonniot-Institut National de la Santé et de la Recherche Médicale, La Tronche, France, and her colleagues (J Clin Onc. 2016 Feb. 1. doi: 10.1200/JCO.2015.63.0970).

In contrast to results from breast cancer studies, TLI did not predict differential survival benefit from adjuvant chemotherapy in NSCLC.

The intensity of TLI on hematoxylin- and eosin-stained representative sections was first assigned into one of four categories (minimal, mild, moderate, and intense). The first three categories subsequently were collapsed into one to form a binary scoring system of intense and nonintense infiltration.

# Crizotinib bests chemo for controlling brain metastases

BY MARY ANN MOON  
Frontline Medical News

**C**rizotinib achieved better control of brain metastases than chemotherapy in a manufacturer-sponsored international open-label phase III randomized trial involving 343 patients with advanced non-small-cell lung cancer (NSCLC), according to a report published March 28 in the Journal of Clinical Oncology.

Even though targeted therapies have greatly improved outcomes for patients whose NSCLC is

alive at 2 years with EGFR- [epidermal growth factor receptor]-mutated or ALK- [anaplastic lymphoma kinase]-rearranged lung cancer will have brain metastases," according to Dr. Benjamin J. Solomon of the department of medical oncology, Peter MacCallum Cancer Centre, Melbourne, and his associates.

They compared the efficacy of intracranial disease control between oral crizotinib and IV pemetrexed-platinum chemotherapy in patients who had advanced nonsquamous ALK-positive NSCLC. A total of 79 of these patients (23%) had brain metastases at baseline.

At 12 weeks, a significantly higher percentage of patients achieved intracranial disease control with crizotinib (85%) than with chemotherapy (45%), and the same was true at 24 weeks (56% vs. 25%).

Median progression-free survival also was longer with crizotinib, regardless of whether patients had brain metastases at baseline (9 months vs. 4 months) or did not have brain metastases at baseline (11 months vs. 7 months), Dr. Solomon and his associates said (J Clin Oncol. 2016 Mar 28. doi: 10.1200/JCO.2015.63.5888).

Similarly, the overall response rate was significantly higher with crizotinib, regardless of whether patients had brain metastases at baseline (77% vs. 28%) or did not have brain metastases at baseline (74% vs. 50%). In addition, disease progression was less frequent with crizotinib than with chemo-

therapy in the overall patient population (52% vs. 77%), in the subgroup of patients who had brain metastases at baseline (54% vs. 75%), and in the subgroup of patients who did not have brain metastases at baseline (52% vs. 78%).

These findings indicate that crizotinib should be the standard first-line therapy for patients who have advanced ALK-positive NSCLC, whether or not they have brain metastases, the investigators said.

**Brain metastases remain 'a significant clinical problem, resulting in considerable physical and neurocognitive morbidity as well as mortality' in patients with NSCLC.**

associated with oncogenic driver mutations, brain metastases remain "a significant clinical problem, resulting in considerable physical and neurocognitive morbidity as well as mortality."

In addition, as patients live longer because of these targeted treatments, the proportion who have brain metastases rises, "such that up to 50% of patients

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# Immunohistochemistry detects occult metastases

BY JENNIFER SHEPPHARD  
*Frontline Medical News*

In patients with non-small cell lung cancer (NSCLC) designated stage I by conventional histopathology, occult metastases were detected by immunohistochemistry (IHC) staining of cytokeratin in 14% of patients and by reverse transcriptase polymerase chain reaction (RT-PCR) for carcinoembryonic antigen in 69% of patients; however, only IHC-positivity within N2 nodes was correlated with overall survival.

Patients who were IHC-positive within an N2 node had worse overall survival than did IHC-negative patients (HR, 2.04; 95% CI, 1.14 to 3.66); 5-year survival for N2 IHC-positive patients compared with IHC-negative patients was 50% (95% CI, 29.1% to 67.8%) vs. 66.9% (60.9% to 72.2%),  $P = .017$ . Patients who were IHC-positive within N1 nodes had survival similar to that of IHC-negative patients.

Although the majority of patients in the study (69%) had occult me-

tastases by RT-PCR, no relationship

between PCR status and overall survival or disease-free survival emerged from the data.

**'Clearly RT-PCR is more sensitive, but perhaps (carcinoembryonic antigen) is not as specific for NSCLC.'**

Surgical resection in early stage NSCLC yields unpredictable outcomes, and one explanation for this is the presence of occult metastases in regional nodes.

"The presence of (occult metastases) is a logical explanation for tumors that are classified as stage I by conventional histopathology to demonstrate a worse prognosis.

However, the current rigorously designed and executed prospective study only showed a significant difference in survival when N2 nodes demonstrated positivity by IHC, but not by RT-PCR," wrote Dr. Linda W. Martin of the University of Maryland, Baltimore, and colleagues (J Clin Oncol. 2016 Feb 29. doi: 10.1200/JCO.2015.63.4543).

"Clearly RT-PCR is more sensitive, but perhaps (carcinoembryonic antigen) is not as specific for NSCLC and thus the clinical im-

pact is insignificant," they wrote.

RT-PCR data showed poor concordance with IHC data in the study, and did not correlate with outcomes, pointing to a lack of clinical utility for RT-PCR in NSCLC.

The Cancer and Leukemia Group B (CALGB) 9761 trial accrued 501 patients from 1997 to 2002, 304 of whom had stage 1A or 1B NSCLC.

Median follow up was 8.4 years (range: 0.97 to 11.4 years).

Local-only recurrence occurred in 24 patients, local and distant in 18, and distant only in 27.

Dr. Martin and her coauthors had no relevant financial disclosures related to their research.



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SPIRIVA RESPIMAT, 1.25 mcg, is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. SPIRIVA RESPIMAT is not indicated for relief of acute bronchospasm.

### IMPORTANT SAFETY INFORMATION

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

SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an attack, a rapid-acting beta<sub>2</sub>-agonist should be used.

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, discontinue SPIRIVA RESPIMAT at once and consider alternative treatments. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT.

Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated with an inhaled short-acting beta<sub>2</sub>-agonist, such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered.



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# Entrectinib proves active in advanced solid tumors

BY DANIEL M. KELLER  
*Frontline Medical News*

**E**ntrectinib, an investigational drug that targets several abnormal fusion proteins, showed

antitumor activity and was safe in patients with several different types of advanced solid tumors.

NTRK1/2/3, ROS1, and ALK gene-rearranged cancers produce fusion proteins that are ligand inde-

pendent for their activity and thus constitutively active, driving tumor growth.

Entrectinib is a pan-TRK, ROS1, ALK tyrosine kinase inhibitor that targets the abnormal fusion protein

products of the genes. It is highly potent at low concentrations, and has been designed to cross the blood-brain barrier (BBB). The targeted proteins are present across multiple

*Continued on following page*

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\*For peak forced expiratory volume in one second (FEV<sub>1,0-3hr</sub>) and trough FEV<sub>1</sub>.

†In clinical trials, an asthma exacerbation was defined as an episode of progressive increase in ≥1 asthma symptom(s) (like shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms) or a decrease of a patient's best morning peak expiratory flow (PEF) of 30% from a patient's mean morning PEF for ≥2 consecutive days that required the initiation or increase in treatment with systemic steroids for ≥3 days.<sup>1</sup>

ICS=inhaled corticosteroids; LABA=long-acting beta<sub>2</sub>-agonist.

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### IMPORTANT SAFETY INFORMATION (continued)

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

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

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

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

The most common adverse reactions >2% incidence and higher than placebo with SPIRIVA RESPIMAT (placebo) in asthma trials in adults were pharyngitis 15.9% (12.4%), sinusitis 2.7% (1.4%), bronchitis 3.3% (1.4%), and headache 3.8% (2.7%).

SPIRIVA RESPIMAT may interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs.

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

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

Reference: 1. SPIRIVA RESPIMAT [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016.

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Continued from previous page

cancers and are especially prevalent (greater than 80%) among some rare adult and pediatric cancers.

The patients studied had never before been exposed to drugs targeting these same genetic alterations.

“Responses can be very rapid and durable ... which include colorectal, primary brain tumor,

astrocytoma, fibrosarcoma, lung, and mammary analog secretory carcinoma,” Dr. Alexander Drilon of Memorial Sloan Kettering Cancer Center in New York said in a news conference at the annual meeting of the American Association for Cancer Research. “Dramatic intracranial activity ... has been demonstrated both in primary brain tumor and also in metastatic.”

Combined data on 119 patients in two phase

I trials established 600 mg orally once daily as the recommended dose to go into phase II trials. Among the 24 patients meeting eligibility criteria for a phase II trial (presence of the targeted gene fusions in their tumors, no prior treatment against these targets, and treatment at or above 600 mg daily), the confirmed response rate was 79% (19/24). Most were partial responses in terms of tumor shrinkage, but two patients had complete

**SPIRIVA® Respimat® (tiotropium bromide) inhalation spray** Rx only  
**FOR ORAL INHALATION**  
**BRIEF SUMMARY OF PRESCRIBING INFORMATION**  
**Please see package insert for full Prescribing Information.**

**INDICATIONS AND USAGE: Maintenance Treatment of Chronic Obstructive Pulmonary Disease:** SPIRIVA RESPIMAT (tiotropium bromide) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA RESPIMAT is indicated to reduce exacerbations in COPD patients. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm. **Maintenance Treatment of Asthma:** SPIRIVA RESPIMAT is a bronchodilator indicated for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. Important Limitation of Use: SPIRIVA RESPIMAT is NOT indicated for the relief of acute bronchospasm.

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

**WARNINGS AND PRECAUTIONS: Not for Acute Use:** SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for COPD and asthma and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. In the event of an acute attack, a rapid-acting beta<sub>2</sub>-agonist should be used. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, therapy with SPIRIVA RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT. **Paradoxical Bronchospasm:** Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta<sub>2</sub>-agonist such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered. **Worsening of Narrow-Angle Glaucoma:** SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects.

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

widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. Since the same active ingredient (tiotropium bromide) is administered to COPD and asthma patients, prescribers and patients should take into account that the observed adverse reactions could be relevant for both patient populations independent of dosage strength. **Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:** The SPIRIVA RESPIMAT clinical development program included ten placebo controlled clinical trials in COPD. Two trials were four-week crossover trials and eight were parallel group trials. The parallel group trials included a three week dose-ranging trial, two 12-week trials, three 48-week trials, and two trials of 4-week and 24-week duration conducted for a different program that contained tiotropium bromide 5 mcg treatment arms. The primary safety database consists of pooled data from the 7 randomized, parallel-group, double-blind, placebo-controlled studies of 4-48 weeks in treatment duration. These trials included 6565 adult COPD patients (75% males and 25% females) 40 years of age and older. Of these patients, 3282 patients were treated with SPIRIVA RESPIMAT 5 mcg and 3283 received placebo. The SPIRIVA RESPIMAT 5 mcg group was composed mostly of Caucasians (78%) with a mean age of 65 years and a mean baseline percent predicted post-bronchodilator FEV<sub>1</sub> of 46%. In these 7 clinical trials, 68.3% of patients exposed to SPIRIVA RESPIMAT 5 mcg reported an adverse event compared to 68.7% of patients in the placebo group. There were 68 deaths in the SPIRIVA RESPIMAT 5 mcg treatment group (2.1%) and 52 deaths (1.6%) in patients who received placebo. The percentage of SPIRIVA RESPIMAT patients who discontinued due to an adverse event were 7.3% compared to 10% with placebo patients. The percentage of SPIRIVA RESPIMAT 5 mcg patients who experienced a serious adverse event were 15.0% compared to 15.1% with placebo patients. In both groups, the adverse event most commonly leading to discontinuation was COPD exacerbation (SPIRIVA RESPIMAT 2.0%, placebo 4.0%) which was also the most frequent serious adverse event. The most commonly reported adverse reactions were pharyngitis, cough, dry mouth, and sinusitis (Table 1). Other adverse reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, dysuria, and urinary retention.

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

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

\*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT 5 mcg group at an incidence of 1% to 3% and at a higher incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo included: *Cardiac disorders:* palpitations; *Gastrointestinal disorders:* constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders:* dizziness; *Respiratory system disorders (Upper):* dysphonia; *Skin and subcutaneous tissue disorders:* pruritus, rash; *Renal and urinary disorders:* urinary tract infection. *Less Common Adverse Reactions:* Among the adverse reactions observed in the clinical trials with an incidence of <1% and at a higher

incidence rate on SPIRIVA RESPIMAT 5 mcg than on placebo were: dysphagia, gingivitis, intestinal obstruction including ileus paralytic, joint swelling, dysuria, urinary retention, epistaxis, laryngitis, angioedema, dry skin, skin infection, and skin ulcer. **Clinical Trials Experience in Asthma: Adult Patients:** SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in four placebo-controlled parallel-group trials ranging from 12 to 52 weeks of treatment duration in adult patients (aged 18 to 75 years) with asthma. The safety data described below are based on one 1-year, two 6-month and one 12-week randomized, double-blind, placebo-controlled trials in a total of 2849 asthma patients on background treatment of at least ICS or ICS and long-acting beta agonist (ICS/LABA). Of these patients, 787 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 59.7% were female and 47.5% were Caucasian with a mean age of 43.7 years and a mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) of 90.0% at baseline. Table 2 shows all adverse reactions that occurred with an incidence of >2% in the SPIRIVA RESPIMAT 2.5 mcg treatment group, and a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo.

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

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

\*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT 2.5 mcg group at an incidence of 1% to 2% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo included: *Nervous system disorders:* dizziness; *Gastrointestinal disorders:* oropharyngeal candidiasis, diarrhea; *Respiratory system disorders (Upper):* cough, rhinitis allergic; *Renal and urinary disorders:* urinary tract infection; *General disorders and administration site conditions:* pyrexia; and *Vascular disorders:* hypertension. *Less Common Adverse Reactions:* Among the adverse reactions observed in the clinical trials with an incidence of 0.5% to <1% and at a higher incidence rate on SPIRIVA RESPIMAT 2.5 mcg than on placebo were: palpitations, dysphonia, acute tonsillitis, tonsillitis, rhinitis, herpes zoster, gastroesophageal reflux disease, oropharyngeal discomfort, abdominal pain upper, insomnia, hypersensitivity (including immediate reactions), angioedema, dehydration, arthralgia, muscle spasms, pain in extremity, chest pain, hepatic function abnormal, liver function test abnormal. *Adolescent Patients Aged 12 to 17 years:* SPIRIVA RESPIMAT 2.5 mcg has been compared to placebo in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in adolescent patients with asthma. The safety data described below are based on one 1-year and one 12-week double-blind, placebo-controlled trials in a total of 789 adolescent asthma patients on background treatment of at least ICS or ICS plus one or more controller. Of these patients, 252 were treated with SPIRIVA RESPIMAT at the recommended dose of 2.5 mcg once-daily; 63.9% were male and 95.6% were Caucasian with a mean age of 14.3 years and a mean post-bronchodilator percent predicted FEV<sub>1</sub> of 98.3% at baseline. The adverse reaction profile for adolescent patients with asthma was comparable to that observed in adult patients with asthma. SPIRIVA RESPIMAT 5 mcg also has been compared to placebo in seven placebo-controlled parallel-group trials ranging from 12 to 52 weeks of treatment duration in

responses. Response rates appeared to vary according to the specific fusion protein defect.

All three cases of CNS disease with NTRK-rearranged cancers had intracranial responses, demonstrating that the drug crosses the BBB and is active. In one case, a 46-year-old man with brain metastases heavily pretreated for non-small cell lung cancer with an NTRK1 rearrangement experienced a dramatic response.

“The patient at that point was actually on hospice and

## Responses to entrectinib in cancers with targeted fusion proteins

Fusion	Confirmed responses (n)	Objective response rate
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

**Note:** The 24 patients met eligibility criteria for a phase II study from an initial phase I open-label dose-escalation study of 119 patients.

**Source:** Dr. Drilon

FRONTLINE MEDICAL NEWS

4149 adult patients (aged 18 to 75 years) with asthma and in two placebo-controlled parallel-group trials ranging from 12 to 48 weeks of treatment duration in 789 adolescent patients (1370 adults and 264 adolescents receiving SPIRIVA RESPIMAT 5 mcg once-daily). The adverse reaction profile for SPIRIVA RESPIMAT 5 mcg in patients with asthma was comparable to that observed with SPIRIVA RESPIMAT 2.5 mcg in patients with asthma. **Postmarketing Experience:** In addition to the adverse reactions observed during the SPIRIVA RESPIMAT clinical trials in COPD, the following adverse reactions have been identified during the worldwide use of SPIRIVA RESPIMAT 5 mcg and another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder): glaucoma, intraocular pressure increased, vision blurred, atrial fibrillation, tachycardia, supraventricular tachycardia, bronchospasm, glossitis, stomatitis, dehydration, insomnia, hypersensitivity (including immediate reactions), and urticaria.

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

**USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects:** Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential

risk to the fetus. No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m<sup>2</sup> basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 40 times the MRHDID (on a mcg/m<sup>2</sup> basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 430 times the MRHDID (on a mcg/m<sup>2</sup> basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m<sup>2</sup> basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). **Labor and Delivery:** The safety and effectiveness of SPIRIVA RESPIMAT has not been studied during labor and delivery. **Nursing Mothers:** Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA RESPIMAT is administered to a nursing woman. **Pediatric Use:** The safety and efficacy of SPIRIVA RESPIMAT 2.5 mcg have been established in adolescents (aged 12 to 17 years) with asthma in 3 clinical trials up to 1 year in duration. In the 3 clinical trials, 327 patients aged 12 to 17 years with asthma were treated with SPIRIVA RESPIMAT 2.5 mcg. Patients in this age group demonstrated efficacy results similar to those observed in patients aged 18 years and older with asthma. The adverse drug reactions profile for this age group was comparable to that observed for patients aged 18 years and older with asthma. Based on available data, no adjustment of dosage of SPIRIVA RESPIMAT in

adolescent patients with asthma is warranted. The safety and efficacy of SPIRIVA RESPIMAT have not been established in pediatric patients less than 12 years of age. **Geriatric Use:** Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted. Thirty nine percent of SPIRIVA RESPIMAT clinical trial patients with COPD were between 65 and 75 years of age and 14% were greater than or equal to 75 years of age. Approximately seven percent of SPIRIVA RESPIMAT clinical trial patients with asthma were greater than or equal to 65 years of age. The adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Renal Impairment:** Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [see Warnings and Precautions]. **Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. **OVERDOSAGE:** High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. Treatment of overdosage consists of discontinuation of SPIRIVA RESPIMAT together with institution of appropriate symptomatic and/or supportive therapy.

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was doing extremely poorly on supplemental oxygen,” Dr. Drilon said. “Within a few weeks, the patient had a dramatic clinical response to therapy ... At day 26 there was almost a 50% reduction in tumor burden.” At day 317 scans showed he had a complete intracranial response to entrectinib, but he still has visceral disease on therapy past 1 year.

Responses often occurred within the first month of therapy, and many persisted for several months without disease progression, with one patient being followed for more than 2 years with clinical benefit. Nineteen of 24 patients have been on the therapy for more than 6 months, and the therapy appears to be safe and well tolerated.

**All three cases of CNS disease with NTRK-rearranged cancers had intracranial responses, demonstrating that the drug crosses the blood brain barrier and is active.**

Commenting on this study and others targeting specific genetic alterations leading to cancer, Dr. Louis Weiner, director of the Georgetown Lombardi Comprehensive Cancer Center in Washington, said, “You’re seeing a series of clinical trials described that aren’t necessarily targeting people with a particular cancer but rather people who have cancers characterized by particular molecular abnormalities.” Not all cancers will have identified molecular abnormalities driving them. “However, I think where you have these drivers, the proper thing to do is not to worry about whether [a drug] works in a given disease but rather whether it works for people with that particular abnormality,” he said.

For the future, the investigators plan a phase II trial called STAR-TRK-2. It is a multicenter, open-label, global basket study to include any solid tumors with the targeted rearrangements.

Dr. Drilon disclosed ties with Ignyta, which funded the study, and has received research funding from Foundation Medicine. Dr. Weiner disclosed ties with several pharmaceutical companies.

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Reference: 1. Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. *Langmuir*. 2012;28(42):15015-15023.

# Lung impedance measures cut HF hospitalizations

BY MITCHEL L. ZOLER

CHICAGO – Regular assessment of a heart failure patient's lung fluid volume using a device that measures electrical conduction through the chest – lung impedance – helped guide clinicians to make timely adjustments in a patient's medications and thereby significantly reduce mortality and hospitalizations during an average 4 years of follow-up in a randomized, controlled study with 256 patients.

Monthly measurement of lung impedance and medication adjustments based on the information led to a 58% reduction in hospitalizations for acute heart failure during the first year of the study, compared with control patients, and a 56% reduction in heart failure hospitalizations, compared with controls, during the entire course of the study, the study's two primary endpoints, Dr. Michael K. Shochat reported at the annual meeting of the American College of Cardiology.

The results also showed that performing regular lung impedance measurements and using the results to guide treatment led to a 43% reduction in all-cause mortality and a 62% drop in heart failure mortality during the average 4-year course of the study, said Dr. Shochat, a cardiologist at the Heart Institute of Hillel Yaffe Medical Center in Hadera, Israel. Concurrent with Dr. Shochat's report at the meeting the results also appeared in an article published online (*J Card Fail.* 2016;doi:10.1016/j.cardfail.2016.03.015).

A key aspect of the study was that the clinicians who treated the enrolled patients who underwent lung impedance monitoring used this information to adjust medications the patients received. Overall, patients who underwent monitoring had more than twice the number of medication dose adjustments, compared with the control patients.

These adjustments particularly focused on diuretic dosages, which changed three times as often in the monitored patients, compared with controls, Dr. Shochat reported. Changes in the dosages of beta-blockers and ACE inhibitors also showed marked increases in the monitored patients, compared with the controls.

The Non-Invasive Lung IMPEDANCE-Guided Preemptive Treatment in Chronic Heart Failure Patients (IMPEDANCE-HF) trial enrolled



**In patients monitored with lung impedance measures, diuretic dosages changed three times as often they did in control patients, Dr. Shochat said.**

256 patients at two centers in Israel during 2005-2014. Patients had New York Heart Association class II-IV heart failure and a left ventricular ejection fraction of 35% or less. The enrolled patients averaged 67 years of age, and 80% were men.

Clinicians measured lung imped-

ance using a proprietary device that places external electrodes on opposite sides of the patient's chest. The calculation of impedance used a formula that eliminated the noise from chest wall impedance and focused exclusively on lung impedance.

Once the electrodes are placed, col-

lection of the impedance data takes about 1 minute, according to Dr. Shochat.

The study protocol called for impedance data to be collected monthly, and in practice it occurred about 11 times a year during the study.

The investigators calculated for each patient in the active arm of the study a "basal" lung impedance level that reflected their level of lung conductivity when their lungs were clear of excess fluid. Participating clinicians were instructed to intervene by altering medications when the impedance level dropped more than 18% below the basal level. Their goal was to prevent impedance from dropping to more than 24% below the basal level, which correlated with when heart failure patients usually required hospitalization for acute decompensation.

IMPEDANCE-HF was sponsored by the RSMM Company, which is developing the lung impedance device used in the study.

Dr. Shochat is a cofounder of RSMM and is a member of the company's board of directors.

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## VIEW ON THE NEWS

### Exciting results depend on physician action

**T**he very exciting results reported by Dr. Shochat came from a small, positive trial that showed impedance monitoring was an effective way to detect an increased amount of fluid in a heart failure patient's lungs. This resulted in improved outcomes, compared with patients managed using usual care, including fewer hospitalizations and reduced mortality.

These results suggest that when physicians had lung impedance information, they identified episodes of acute heart failure decompensation sooner and that they used this alert to change treatment and prevent patient worsening. Heart failure exacerbations and decompensation events are a recurring problem for heart failure patients, and the earlier they are identified and addressed with altered treatment, the better it is for the patient's well being. The next step is to see if these positive results can be confirmed by other research groups and in larger numbers of patients.

These results contrast with the findings from a German study reported in 2015 that used lung impedance information collected by implantable cardioverter defibrillators in heart failure patients to identify episodes of fluid buildup and decompensation. That study failed to show a statistically significant impact on patient outcomes. The researchers speculated that this may have been because patients often did not go online to allow their information to get transmitted to their physician,

and physicians often did not act on the information because the patients reported no coincident change in symptoms.

This problem with the German study highlights that collecting lung impedance information will only improve outcomes if physicians then act on the information and modify a patient's treatment. In the new study reported by Dr. Shochat, patients consistently underwent evaluation for their lung impedance status every month, and when the results suggested a growing problem of fluid overload the physicians consistently acted on the information by adjusting medication dosages.

Use of lung impedance measurement is similar to another approach for monitoring patients with heart failure that recently entered routine U.S. practice, an implanted device to monitor pulmonary artery pressure and identify episodes of fluid overload and acute decompensation. In the future, it will be interesting to compare the efficacy and ease of use of managing heart failure patients with pulmonary artery pressure monitoring with an implanted device and monitoring fluid build up in the lungs with lung impedance.

*Dr. John A. Jarcho is a cardiologist at Brigham and Women's Hospital, Boston. He had no disclosures. He made these comments as a discussant of Dr. Shochat's report and in an interview.*

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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  $\alpha$ -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.

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sildenafil

### 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 anatomical 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<sup>2</sup> 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<sup>2</sup> 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 CL<sub>Cr</sub> <30 mL/min).

#### PATIENT COUNSELING INFORMATION

- Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.
- Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.
- Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.
- Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only

Rev. June 2015

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# Coronary artery calcium linked to COPD risk

BY AMY KARON  
Frontline Medical News

Patients whose coronary artery calcium scores exceeded 400 were significantly more likely to develop cancer, chronic obstructive pulmonary disease, chronic kidney disease, and hip fractures, compared with adults with undetectable CAC, in an analysis of the Multi-Ethnic Study of Atherosclerosis reported March 9 in JACC Cardiovascular Imaging.

The study is the first to examine the relationship between CAC and significant noncardiovascular diseases, said Dr. Catherine Handy of the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore. Patients with CAC scores of zero represent a unique group of “healthy agers,” she and her associates said. Conversely, 20% of initial non-CVD events occurred in the 10% of patients with CAC scores over 400, and 70% of events occurred in patients with

scores greater than zero, they reported.

While CAC is an established indicator of vascular aging, CVD risk, and all-cause mortality, its relationship with non-CVD is unclear. To



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elucidate the issue, the researchers analyzed data from the prospective, observational Multi-Ethnic Study of Atherosclerosis, which included 6,814 adults aged 45-84 years from six U.S. cities. Patients had no CVD and were not receiving cancer treatment.

*Continued on following page*

#### VIEW ON THE NEWS

### CAC is global marker of health

The current report from the Multi-Ethnic Study of Atherosclerosis further expands the evidence base supporting the concept of coronary artery calcium as a marker of global health by examining its prognostic power across a diversity of noncardiovascular conditions.

Regardless of the directionality or magnitude of the connections between cardiovascular disease and non-CVD conditions, the extent to which coronary artery calcium-guided patient adherence to risk factor modification and lifestyle recommendations [affected] non-CVD conditions remains an additional link that should be explored further.

A synthesis of evidence, including the study by Handy et al., now supports the predictive ability of coronary artery calcium to estimate cardiac, cerebrovascular, and noncardiovascular conditions. We likely should come full circle in

our discussion and acknowledge the far reaching implications of its predictive ability. Perhaps our index response that CAC should be fully integrated into all adult wellness and screening evaluations was on target after all!

Although CAC has not been without its critics and is not supported as a reimbursable procedure, its expansive evidence warrants a more thoughtful discussion within the CVD community that this powerful procedure provides valuable information to guide health care decision making.

*Dr. Mosaab Awad, Dr. Parham Esh-tehardi, and Leslee J. Shaw, Ph.D., of Emory University Clinical Cardiovascular Research Institute, Emory University, Atlanta, made these comments in an editorial (JACC Cardiovasc Imaging. 2016 Mar 9. doi: 10.1016/j.jcmg.2015.09.021). They had no disclosures.*

# Rate and rhythm control both effective for post-op AF

BY BRUCE JANCIN  
Frontline Medical News

CHICAGO – Rate and rhythm control proved equally effective for treatment of new-onset post-cardiac surgery atrial fibrillation in a randomized trial that was far and away the largest ever to examine the best way to address this common and costly arrhythmia, Dr. A. Marc Gillinov said at the annual meeting of the American College of Cardiology.

Thus, either strategy is acceptable. That being said, rate control gets the edge as the initial treatment strategy because it avoids the considerable toxicities accompanying amiodarone for rhythm control, most of which arise only after patients have been discharged from the hospital. In contrast, when rate control doesn't work, it becomes evident while the patient is still in the hospital, according to Dr. Gillinov, a cardiothoracic surgeon at the Cleveland Clinic.

Atrial fibrillation (AF) is the most common complication of cardiac surgery, with an incidence variously reported at 20%-50%. It results in lengthier hospital stays, greater cost of care, and increased risks of mortality, stroke, heart failure, and infection. Postoperative AF adds an estimated \$1 billion per year to health care costs in the United States.

While current ACC/AHA/Heart Rhythm Society joint guidelines recommend rate control with a beta-blocker as first-line therapy for patients with this postoperative complication, with a class I, level-of-evidence A rating, upon closer inspection the evidence cited mainly involves extrapolation from studies looking at how to prevent postoperative AF. Because no persuasive evidence existed as to how best to treat this common and economically and medically costly condition, Dr. Gillinov and his coinvestigators in the National Institutes of Health-funded Cardiothoracic Surgical Trials Net-

work carried out a randomized trial 10-fold larger than anything prior.

The 23-site study included 2,109 patients enrolled prior to cardiac surgery, of whom 40% underwent isolated coronary artery bypass grafting (CABG) while the other 60% had valve surgery, either alone or with CABG. These proportions reflect current cardiac surgery treatment patterns nationally. Overall, 33% of the cardiac surgery patients experienced post-operative AF. The incidence was 28% in patients who underwent isolated CABG but rose with increasing surgical complexity to nearly 50% in patients who had combined CABG and valve operations. The average time to onset of postoperative AF was 2.4 days.

DR. GILLINOV

A total of 523 patients with postoperative AF were randomized to rate or rhythm control. Rate control most often entailed use of a beta-blocker, while amiodarone was prescribed for rhythm control.

The primary endpoint in the trial was a measure of health care resource utilization: total days in hospital during a 60-day period starting from the time of randomization. This endpoint was a draw: a median of 5.1 days with rate control and 5.0 days with rhythm control.

At hospital discharge, 89.9% of patients in the rate control group and 93.5% in the rhythm control group had a stable heart rhythm without AF. From discharge to 60 days, 84.2% of patients in the rate control group and a similar 86.9% of the rhythm control group remained free of AF.

Rates of serious adverse events were similar in the two groups: 24.8 per 100 patient-months in the rate control arm and 26.4 per 100 patient-months in the rhythm control arm. Three patients in the rate control arm died during the 60-day study period, and two died in the rhythm control group.

Of note, roughly one-quarter of patients in each study arm crossed over to the other arm. In the

rate control group, this was typically due to drug ineffectiveness, while in the rhythm control arm the switch was most often made in response to amiodarone side effects.

Roughly 43% of patients in each group were placed on anticoagulation with warfarin for 60 days according to study protocol, which called for such action if a patient remained in AF 48 hours after randomization.

There were five strokes, one case of transient ischemic attack, and four noncerebral thromboembolisms. Also, 21 bleeding events occurred, 17 of which were classified as serious; 90% of the bleeding events happened in patients on warfarin.

"I found the results very striking and very reassuring," said discussant Hugh G. Calkins. "To me, the clinical message is clearly that rate control is the preference."

It was troubling, however, to see that 10 thromboembolic events occurred in 523 patients over the course of just 60 days. "Should we be anticoagulating these postsurgical atrial fibrillation patients a lot more frequently?" asked Dr. Calkins, professor of medicine and of pediatrics and director of the cardiac arrhythmia service at Johns Hopkins University, Baltimore.

Dr. Gillinov replied that he and his colleagues in the Cardiothoracic Surgical Trials Network consider that to be the key remaining question regarding postoperative AF. They are now planning a clinical trial aimed at finding the optimal balance between stroke protection via anticoagulation and bleeding risk.

The National Institutes of Health and the Canadian Institutes of Health Research funded the work. Dr. Gillinov reported serving as a consultant to five surgical device companies, none of which played any role in the study.

Simultaneously with Dr. Gillinov's presentation at ACC 16, the study results were published in the *New England Journal of Medicine* (doi: 10.1056/NEJMoa1602002).

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**Rate control gets the edge as it avoids the toxicities accompanying amiodarone for rhythm control.**

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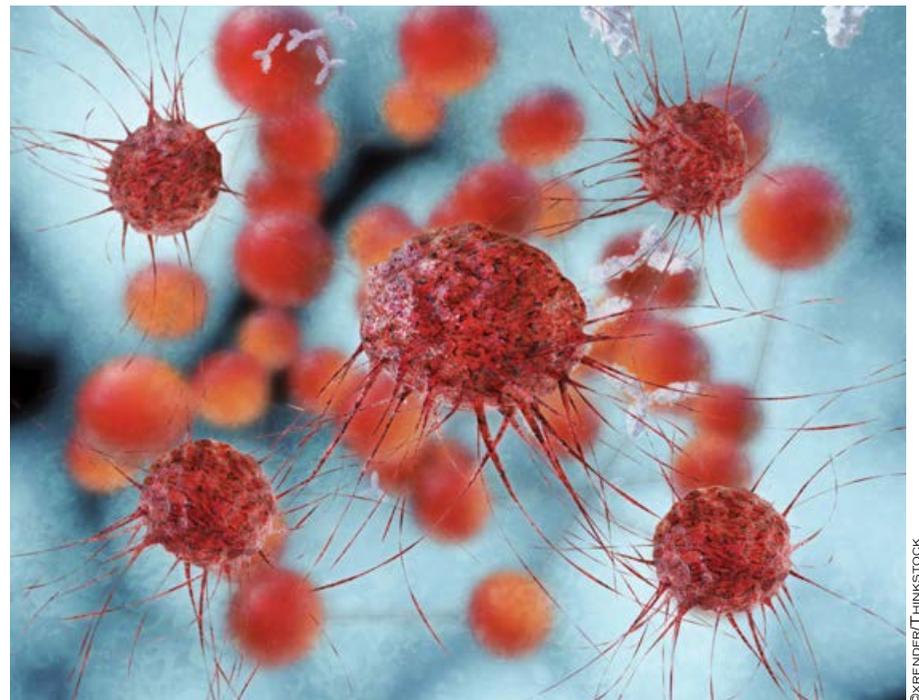
Over a median follow-up period of 10.2 years, and after controlling for demographic factors and predictors of CVD, patients with CAC scores exceeding 400 were significantly more likely to develop cancer (hazard ratio, 1.53), chronic kidney disease (HR, 1.70), pneumonia (HR, 1.97), chronic obstructive pulmonary disease (HR, 2.71) and hip fracture (HR, 4.29), compared with patients without detectable CAC. Patients with CAC scores of zero were at significantly lower risk of these diagnoses, compared with patients with scores greater than zero (JACC Cardiovasc Imaging. 2016 Mar 9. doi: 10.1016/j.jcmg.2015.09.02).

Doubling of CAC was a modest

but significant predictor of cancer, chronic kidney disease, pneumonia, and chronic obstructive pulmonary disease in the subgroup of adults aged 65 years and older. However, CAC was not associated with dementia or deep vein thrombosis or pulmonary embolism.

Sparse diagnoses of hip fractures and DVT/PE meant that the study might be underpowered to clearly link CAC with risk of these events, said the researchers. There also might not have been enough follow-up time to uncover risk in participants with the lowest CAC scores, they said. "At this time, our data are not powered for stratifying results based on gender or race," they added.

The National Institutes of Health funded the study. The researchers had no conflicts of interest.



# Guideline harmonizes DAPT duration after stenting

BY AMY KARON  
Frontline Medical News

New guidelines decrease the minimum duration of dual-antiplatelet therapy (DAPT) to as little as 3 months after drug-eluting stent placement in certain lower-risk patients with coronary artery disease.

The updated recommendations harmonize and replace six other guidelines, and apply to everolimus and zotarolimus stents, not Cypher or Taxus stents, said Dr. Eric R. Bates, who helped author the Ameri-



**The emphasis is on balancing ischemic risk versus bleeding risk. Clinicians can personalize DAPT.**

DR. BATES

can College of Cardiology/American Heart Association Focused Update. “The emphasis is on balancing ischemic risk versus bleeding risk. The recommendations give clinicians guideline coverage to make personalized DAPT recommendations,” he said in an interview.

The guidance reflects recent evidence that shorter duration (3-6 months) of DAPT, compared with the standard 12 months of therapy does not increase the risk of stent thrombosis and potentially lessens bleeding risk in select patients. Other studies of an additional 18 or 36 months of DAPT found a decrease in the risk of MI and stent thrombosis, at the cost of greater risk of bleeding. Thus, the updated guidelines call for “a thoughtful assessment of the benefit-risk ratio, integration of study data, and consideration of patient preference” when selecting duration of DAPT. “In general, shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk,” the authors wrote, led by Dr. Glenn N. Levine of Baylor College of Medicine, Houston (J Am Coll Cardiol. 2016 Mar 29. doi: 10.1016/j.jacc.2016.03.512).

The recommendations define DAPT as combination therapy with aspirin and a P2Y12 receptor inhibitor – that is, clopidogrel, prasugrel, or ticagrelor. “When indicated, ticagrelor and prasugrel have a Class

Ia preference over clopidogrel,” Dr. Bates said. The recommended daily dose of aspirin is 81 mg (range, 75-100 mg), which is usually continued indefinitely, regardless of how long patients receive dual therapy.

The shortened durations of dual-antiplatelet therapy include several scenarios. For elective percutaneous coronary intervention, the former Class I recommendation for 12 months of DAPT has been reduced to 6 months, with a Class IIb recommendation for either longer treatment or shorter (3-month) treatment, Dr. Bates, professor of medicine at the University of Michigan Health System in Ann Arbor, said. For patients with acute coronary syndrome, the guidelines retain the Class I recommendation for 12 months of DAPT, but also add a Class IIb recommendation for longer or shorter (6 months) DAPT.

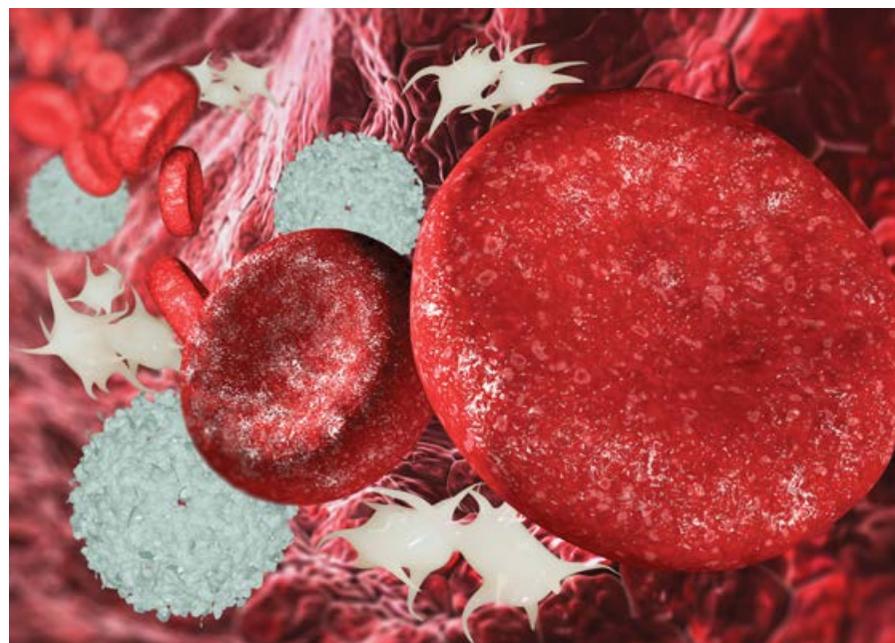
The guidelines also include a new Class IIb recommendation for 12 months of DAPT started early after coronary artery bypass graft in patients with stable ischemic heart disease. This strategy “may be reasonable to improve vein graft patency” in these patients, the recommendations state.

The guidance clarifies previous recommendations on the timing of elective noncardiac surgery, and assigns Class IIb support for consideration of such surgeries starting 3 months after implantation of drug-eluting stents, if the risks of delaying surgery outweigh the expected risk of stent thrombosis when it is necessary to stop P2Y12 inhibitor therapy.

The recommendations now distinguish between B and C levels of evidence to increase granularity, according to Dr. Bates. The document updates recommendations on duration of DAPT across six previously published guidelines – the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (PCI); the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery; the 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease; the 2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction; the 2014 ACC/AHA Guideline for Non-ST-Elevation Acute Coronary Syndromes, and the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery.

The extensive evidence review that informed guideline development was simultaneously reported by Dr. John Bittl at Munroe Regional Medical Center in Ocala, Fla., and his colleagues. The investigators synthesized evidence from 11 randomized controlled trials of more than 33,000 patients who received mainly newer generation stents. They also reviewed a randomized controlled trial of

in stent thrombosis and MI and increases in major hemorrhage,” Dr. Bittl and his colleagues wrote. Likewise, they found moderately strong evidence that prolonged DAPT helps prevent cardiovascular events at the cost of increased bleeding in patients whose coronary thrombotic risk stemmed from prior MI, not stent implantation. They found weak evidence of increased mortality in stent



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more than 21,000 patients with stable ischemic heart disease who were more than 1 year post-MI, and a post hoc analysis of a trial of more than 15,000 such patients.

These reviews uncovered “moderately strong evidence” that prolonged DAPT after implantation of newer generation drug-eluting stents “entails a trade-off between reductions

patients who received prolonged DAPT.

Dr. Bates reported consulting relationships with Merck and AstraZeneca. Eight other coauthors disclosed financial relationships with a number of pharmaceutical or device companies. Dr. Glenn Levine and seven coauthors disclosed no relationships with industry.

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# 24-hour BREO—Approved for Asthma

For adult patients with asthma uncontrolled on an ICS or whose disease severity clearly warrants an ICS/LABA. BREO is NOT indicated for the relief of acute bronchospasm.

## Important Safety Information

### WARNING: ASTHMA-RELATED DEATH

- **Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, only prescribe BREO for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO for patients whose asthma is adequately controlled on low- or medium-dose ICS.**

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.
- BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.
- Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.
- Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.

### WARNINGS AND PRECAUTIONS (cont'd)

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.
- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents.

### ADVERSE REACTIONS

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

### DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, 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.



BREO ELLIPTA was developed in collaboration with  Theravance

# Reach for BREO

YOU WANT...

**24**-hour efficacy

SHE WANTS...

**1** daily dose

## Reach With Confidence

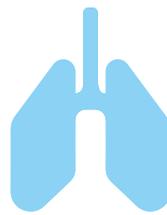
In patients uncontrolled on an ICS alone, BREO has been proven to:

Deliver 24-hour lung function improvement



with one inhalation, once daily\*

Reduce asthma exacerbations



in patients with a history of exacerbations†

Increase days without asthma symptoms



and increase days without use of rescue medication‡

### Important Safety Information (cont'd)

#### DRUG INTERACTIONS (cont'd)

- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non-potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.

#### USE IN SPECIFIC POPULATIONS

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

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

### Supporting Clinical Study Information

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

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

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

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

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

Visit [BREOhcp.com](http://BREOhcp.com) for more information, including Patient Assistance Programs.

**BREO**<sup>®</sup> ELLIPTA<sup>®</sup>  
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

## BRIEF SUMMARY

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

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

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

### WARNING: ASTHMA-RELATED DEATH

**Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**

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

## 1 INDICATIONS AND USAGE

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

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

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

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

**5.2 Deterioration of Disease and Acute Episodes** BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO has not been studied in subjects with acutely deteriorating COPD or asthma. The initiation of BREO in this setting is not appropriate. Increasing use of inhaled, short-acting beta<sub>2</sub>-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<sub>2</sub>-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-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<sub>2</sub>-agonist and instruct the patient on how it should be used.

**5.3 Excessive Use of BREO and Use with Other Long-Acting Beta<sub>2</sub>-Agonists** BREO should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using BREO should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

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

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

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

almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies. During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO. Lung function (FEV<sub>1</sub> 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, troleanandomycin, 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<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**5.13 Reduction in Bone Mineral Density** Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

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

**5.15 Coexisting Conditions** BREO, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

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

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

## 6 ADVERSE REACTIONS

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

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

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

In Trial 1, adverse reactions (≥2% incidence and more common than placebo) reported in subjects with asthma taking BREO 100/25 (n=201) (fluticasone furoate 100 mcg [n=205] or placebo [n=203]) were: nasopharyngitis,

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

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

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

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

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

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

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

**Cardiac Disorders** Palpitations, tachycardia.

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

**Musculoskeletal and Connective Tissue Disorders** Muscle spasms.

**Nervous System Disorders** Tremor.

**Psychiatric Disorders** Nervousness.

## 7 DRUG INTERACTIONS

**7.1 Inhibitors of Cytochrome P450 3A4** Fluticasone furoate and vilanterol, the individual components of BREO, are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleanandomycin, 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  $\beta_2$ -agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

**7.4 Non-Potassium-Sparing Diuretics** The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  $\beta_2$ -agonists, especially when the recommended dose of the  $\beta_2$ -agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of  $\beta_2$ -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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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  $\beta_2$ -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 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  $\beta_2$ -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  $\beta_2$ -adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of  $\beta_2$ -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.

**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  $\beta_2$ -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.

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BREO was developed in collaboration with Theravance 



GlaxoSmithKline  
Research Triangle Park, NC 27709

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## PRESIDENT'S REPORT Who's running the show?

**DR. BARBARA PHILLIPS,**  
MSPH, FCCP

CHEST President 2015-2016

**NANCY MACRAE**

Senior Vice President, Governance and Operations

**JENNY NEMKOVICH, CAE**

Chief Strategy Officer, Executive Office

Ever wonder how decisions get made and work gets done at CHEST? It all starts with our strategic plan ([www.chestnet.org/About/Overview/Strategic-Plan](http://www.chestnet.org/About/Overview/Strategic-Plan)), which was developed by the Board of Regents and other key stakeholders. The development of the strategic plan was informed by our vision to be the global leader in advancing best patient outcomes through innovative chest medicine, education, clinical research, and team-based care, as well as our mission and values. As a result of our strategic planning, CHEST is all about clinical education, which is our “hedgehog,” in organization-speak,<sup>1</sup> but we also have goals in guideline development, global impact, membership recruitment and retention, and (of course) fiscal health. We follow progress toward our goals with measurable, relevant key performance indicators (KPIs), and the board reviews progress toward KPIs and goals at nearly every meeting, making recommendations for adjustments, as needed.

But how do decisions get made? CHEST volunteer and staff leader-

ship work together to initiate and execute projects consistent with our plan and respond to requests from others to explore collaborative opportunities to advance our goals.

An example of a process that was initiated by leadership was the development of our new membership model. The Community and Engagement Work Group, along with key staff and other stakeholders, reviewed environ-



DR. PHILLIPS

mental scans, their personal knowledge and situations, and data from surveys of CHEST members, as well as association trends. They then proposed a new membership model to the Board of Regents (BoR). The BoR reviewed the proposal, along with other important information, and expressed concerns about several key

constituent groups, such as global members and members-in-training, along with several other issues. In fact, the BoR sent the proposal back to the Work Group. Twice. As with any new project, the BoR makes a concerted effort to focus on the strategic plan in these types of deliberations and was guided particularly by the strategy to “optimize new membership model to increase engagement of all clinicians on the health-care team.” The final proposal, implemented in May 2015, truly reflects input and concerns from the BoR, key staff, the Membership Committee, and those CHEST members who responded to the surveys.

An example of a request by another



CHEST Board of Regents 2015-2016

organization to sign on, endorse, cosponsor, or otherwise support a guideline or project is the Campaign for Tobacco-Free Kids contacting us asking us to sign on to a letter to all members of the United States Senate and House of Representatives supporting the tobacco control measure included in the Trans-Pacific Partnership (TPP) trade agreement. The provision will protect the rights of nations participating in the TPP to adopt public health measures that reduce tobacco use without fear of facing lengthy and expensive trade disputes under the TPP initiated by tobacco companies.

Our process in these situations is to gather as much input as possible from CHEST members and experts. Again, using our strategic plan as guidance, in this specific instance, we are expanding our global impact, using targeted strategic alliances, so the decision was made to support

this initiative. The CHEST name and brand are valuable assets, and we take endorsement of any project or document very seriously.

Key to our organizational success is our outstanding volunteer/staff partnership that fosters teamwork in translating the strategic vision, mission, and goals of the organization, engaging in a deliberative process that considers organizational history, data, trends, and expert opinion – all to help inform leadership in its decision-making. This collaboration between our content experts and our association professionals is a huge asset to our organization and one that will continue to propel CHEST to achieve our goals.

### Reference

1. Collins J. *Good to Great and the Social Sectors: A Monograph to Accompany Good to Great*. New York, NY: Harper-Collins Publishers; 2005.

## 2016 NetWorks Challenge

In March, the foundation kicked off the 2016 NetWorks Challenge, and we're delighted to see a very enthusiastic response from our NetWorks Steering Committee members. In fact, we are thrilled to announce that the first NetWorks Steering Committee to achieve 100% participation is the Women's Health NetWork. Every member on the steering committee made a donation to the CHEST Foundation last month.

“Physicians are competitive by nature and always welcome a challenge; the CHEST Foundation challenge is no exception,” stated Dr. Ghada Bourjeily, FCCP, Chair of the Women's Health NetWork. “The Women's Health NetWork Steering Committee members jumped on the opportunity to donate as soon as they heard

about this great opportunity and donated to the CHEST Foundation.”

This year, the prizes for winning the NetWorks Challenge are more enticing than ever before. In the first round, the highest percentage of participation by a NetWork Steering Committee will receive additional time for the NetWorks Featured Lecture at CHEST 2016. And, for the very first time, the CHEST Foundation is offering up to two travel grants to CHEST 2016. In the second round, the top two NetWorks Steering Committees that are able to contribute the highest total amount will receive a seat on the CHEST Foundation's Awards Committee and a potential clinical research grant. Up to two travel grants to CHEST 2017 will also be awarded in the final round to the NetWork that has the highest



percentage of participation among its membership.

Dr. David Schulman, MPH, FCCP, Chair of the Council of NetWorks, recently commented on why it is critical to take part in the NetWorks Challenge: “Participating in the Net-

Works Challenge will serve many great purposes. First, it's an opportunity to give to a great organization that does fantastic work. Second, if you're a member of a NetWork and you participate, it allows your NetWork to achieve greatness. How? Because you get extra time at the annual meeting to show off your wares to your members by letting your national leaders speak to your members. Third, you can get travel grants for your colleagues, which allow them to attend the annual meeting at no cost. Fourth, you can participate in awarding grants to next year's foundation awardees as a public member of the CHEST Foundation Awards Committee. In short, there is no reason not to give to the foundation as part of the NetWorks Challenge.”

## Recharge in Los Angeles

When you imagine Los Angeles, you probably envision images of glamorous Hollywood celebrities and ritzy beaches featured on television shows. While LA does, indeed, allure visitors with its high-end environment, there are also many opportunities to unwind and recharge in the Golden State. With mild temperatures and sunshine nearly 300 days a year, Los Angeles provides a haven for outdoor activities. While you're attending CHEST 2016 from October 22 to 26, we encourage you to trade your stilettos for hiking boots or athletic shoes, and get outside during your free time.

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2016

The San Gabriel Mountains are about an hour's drive from the Los Angeles Convention Center. Visitors can hike, picnic, and enjoy equestrian trails. Our favorite LA experts – CHEST members – have recommended renting a mountain bike and riding up to Mount Wilson. You can also hike the Eaton Canyon Trail and find the Eaton Canyon Waterfall, a 40-foot waterfall with a pool at its base. You can find more mountain ranges and hiking opportunities in the Santa Monica mountains, as well. Find more tips on trails and hiking at [discoverlosangeles.com](http://discoverlosangeles.com).

If you're not interested in retreating from Los Angeles's urban oasis, but you still want to enjoy some fresh air and exercise, you have a couple options closer to downtown. Runyon Canyon is about a 20-minute drive from the convention center. It features a gently paved path for beginners, a rugged outer path for a more intense workout, free yoga near the Fuller Avenue entrance, a great setting for watching the sunset, and strong possibilities of celebrity sightings. You can also rent a bike and cycle along the beaches. You can stop off for a bite to eat, some sand volleyball, or just to do some people watching.

And if you're a golf enthusiast, there is a bevy of options for golfing in and around LA. The most iconic golf course is the Trump National Golf Club located on the Palos Verdes Peninsula, about a 40-minute drive from the convention center. You'll experience uncompromising luxury overlooking the beautiful Pacific Ocean. If you'd like to stay close

to the convention center but still get out to play 9 holes, you may want to check out Wilshire Country Club (20-minute drive) or Monterey Park Golf Club (12-minute drive).

While Los Angeles refreshes

you with outdoor beauty and sunshine, CHEST 2016 will energize and recharge you with the latest information in chest medicine. You'll connect with an international community of the best minds in

pulmonary, critical care, and sleep medicine. Find everything you need to know to make the best clinical decisions and inspire your patient care. Learn more at [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org).



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# CHEST announces a historic collaboration

The American College of Chest Physicians (CHEST) and the Chinese Association of Chest Physicians (CACP), the respiratory arm of the Chinese Medical Doctor Association (CMDA), have signed an exclusive agreement to collaborate on expanding China's first-ever fellowship training program, providing clinical education in pulmonary and critical care medicine (PCCM) for Chinese physicians.

This historic announcement came during the opening session of CHEST World Congress 2016 in Shanghai, where approximately 2,000 health care professionals gathered for a 3-day event aimed at connecting clinicians from the United States, China, and around the world for hands-on clinical education in pulmonary, critical care, and sleep medicine. Among those in attendance were fellows and faculty from the 12 institutions that participated in the inaugural offering of the China-CHEST PCCM program, which was developed and implemented over the past 4 years and is expected to grow to dozens of institutions over the next several years.

Since 2012, CHEST has worked with the Chinese Thoracic Society on the



**Announcing the formal agreement: Dr. Darcy Marciniuk, FCCP (Past President, CHEST); Dr. Chen Wang, PhD, FCCP (President, Chinese Association of Chest Physicians and Chinese Thoracic Society); and Dr. Barbara Phillips, MPH, FCCP (President, CHEST)**

development of China's first fellowship program, offering standardized training in PCCM for Chinese physicians. As a result of these collective efforts, PCCM has now officially earned recognition as a medical subspecialty by the Chinese Ministry of Health – the first subspecialty of its kind in a country where medical training typically ends after a physician completes residency training.

Only a decade ago, physicians in China went directly into practice following medical school. The development of a PCCM subspecialty in China – made possible through the engagement of CHEST's expert faculty and administration – parallels what has occurred over the past 3 decades in the United States, during which the fields of pulmonary and critical care medicine

evolved into the combined subspecialty of PCCM.

Through the collaboration, CHEST and the CACP have committed to working exclusively as partners in continuing to advance the PCCM subspecialty in China to improve patient care, expand in-depth clinical training for Chinese physicians, and develop a growing force of expert Chinese faculty. The goal of such training is to ensure that patients receive the best possible care from Chinese physicians who complete the China-CHEST PCCM fellowship program.

“Recognition by the Chinese Ministry of Health of PCCM as this country's first-ever physician subspecialty is welcomed acknowledgment that we're making tremendous headway in advancing physician fellowship training in China,” said Dr. Barbara Phillips, MPH, FCCP, President of the American College of Chest Physicians. “We are proud to join collaborative partners like the CMDA in these cooperative efforts to prepare Chinese physicians in the PCCM subspecialty, partnering in this historic effort to drive immeasurable improvements in clinical training and the delivery of patient care.”

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Connecting a Global Community in Clinical Chest Medicine



**LOS ANGELES**  
OCTOBER 22 - 26

With mild temperatures and sunshine nearly 300 days a year, Los Angeles is often described as “perfect.” And, it's a perfect setting for CHEST 2016, where we'll connect a global community in clinical chest medicine. As always, our program will deliver current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats.

> Register Now [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org)

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**Advanced Critical Care Echocardiography**  
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Focus on practical elements of advanced critical care echocardiography through hands-on training. Learn practical measurement skills relevant to the diagnosis and management of patients with cardiopulmonary failure.

#### Who Should Attend?

Our live learning ultrasonography courses are ideal for critical care team members interested in enhancing their proficiency in the field. Frontline intensivists, pulmonary/critical care specialists, and fellows; hospitalists; emergency medicine/critical care, anesthesia/critical care, and surgical/critical care fellows; physicians; nurse practitioners; and physician assistants are encouraged to attend.

**NEW! Transesophageal Echocardiography**  
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Learn critical care transesophageal echocardiography (TEE) image acquisition through the use of high fidelity TEE simulators in small group training sessions. Master image interpretation by reviewing large numbers of TEE studies presented in an interactive, case-based format led by international experts in the field.

> Register Now [chestnet.org/live-learning](http://chestnet.org/live-learning)

## Catching up with our Past Presidents

**W**here are they now? What have they been up to? CHEST's Past Presidents each forged the way for the many successes of the American College of Chest Physicians (CHEST), leading to enhanced patient care around the globe. Their outstanding leadership and vision are evidenced today in many of CHEST's current initiatives, and now it is time to check in with one of our past leaders to give us a look at what's happening in her life.

### Dr. Kalpalatha K. Guntupalli, Master FCCP, MACP, FCCM

Frances K. Friedman and Oscar Friedman, MD '36 Endowed Professor for Pulmonary Disorders; and Chief, Section of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Baylor College of Medicine.

### President 2009-2010

November 1, 2009, is clearly etched into my memory. I was sworn in as the 73rd President, and 3rd woman President, of the American College of Chest Physicians during CHEST Annual Meeting 2009 in San Diego.

I consider the 2 years leading up to the presidency and the year following my term as the best years of my professional career. They were action packed, full of excite-

ment that gave immense satisfaction. During my year, the longtime



Dr. Guntupalli

EVP/CEO, Al Lever, retired, and we welcomed the new EVP/CEO Mr. Paul Markowski.

To make the transition easier, I started the "4 Ps" call of the 4 Presidents (President-Designate, President-Elect, President, and the Past President), a weekly call to catch up and keep everyone in the loop. This has since become a tradition in the organization.

My theme for the year was "Act local, Think global." We started many international initiatives, in the Middle East, India, China, and South America, that have since evolved

into successful programs. In 2010, as members of the Federation of International Respiratory Societies (FIRS), we celebrated the "Year of the Lung." We participated in the "world spirometry day" (102,487 spirometries were done globally) and did many other programs to increase awareness of lung disease. We held a long-term strategic retreat developing goals for the College. We implemented many other process-driven initiatives under the new CEO's leadership.

Land was acquired where the new beautiful headquarters building now stands.

### What is life like after CHEST Presidency?

I was very honored in 2012 to receive the "Pravasi Bharatiya Samman," the highest award bestowed on a nonresident Indian by the President of India or distinguished members of the Indian Diaspora to "honor exceptional and meritorious contributions in their chosen field/profession and enhancing the image of India." In 2013, I spent 4 months as a Fulbright Scholar forming an ARDS network in India, and in 2015, I was honored as a Master FCCP by our own organization.

As the Section Chief, I have been busy building a "Lung Institute" and ICU services along with many new initiatives in our very active Pulmonary/CC/Sleep section at Baylor College of Medicine.

## This month in CHEST: Editor's picks

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

### Editorial

#### New Sepsis

#### Criteria:

#### A Change We Should Not

Make. By Dr. S. Q. Simpson.



#### Giants in Chest Medicine

#### Arthur P.

Wheeler, MD, FCCP. By Dr. G. R. Bernard.

#### Topics in Practice Management

#### Update on Exhaled Nitric Oxide in

Clinical Practice. By Dr. S. R. Mummadi and Dr. P. Y. Hahn.

#### Original Research

#### Airway Surfactant Protein D Deficiency in Adults With Severe Asthma. By

Dr. R. A. Mackay et al.

#### Outcomes of Nurse Practitioner-Delivered Critical Care: A Prospective Cohort Study.

By Dr. J. S. Landsperger et al.

## Update on CHEST Clinical Trials Registry

**A**re you a clinical trials investigator with unused capacity? Would you like to refer patients to participate in groundbreaking clinical trials?

The CHEST Clinical Trials Registry is a free service that connects physicians to information about clinical trials in respiratory disease conducted by participating pharmaceutical companies.

Ongoing groundbreaking research could have a measurable impact on patient care, but a lack of clinical trial participants is significantly slowing research and threatening the development of new treatments. Recruiting and retaining trial participants are the greatest challenges to developing the next generation of treatment options.

Participation in clinical trials provides an opportunity to advance and accelerate medical research and contribute to an improved health outlook for future generations. Use our registry to get immediate information on how you can be involved in a clinical trial.

Access to learn more: [chestnet.org/Guidelines-and-Resources/Clinical-Trials/Clinical-Trials-Registry](http://chestnet.org/Guidelines-and-Resources/Clinical-Trials/Clinical-Trials-Registry).

## In Memoriam

**D**r. Lawrence H. Cohn, FCCP, a Past President of the American College of Chest Physicians (1986-87), pioneering cardiac surgeon and devoted educator, former chief of the Division of Cardiac Surgery at Brigham and Women's Hospital, and the Virginia and James Hubbard Chair in Cardiac Surgery at Harvard Medical School, died Jan. 9, 2016.

An internationally renowned surgeon, he was a pioneer in minimally invasive procedures to fix heart valves. He also performed more than 11,000 cardiac surgeries, including being part of the team for New England's first heart transplant, which took place at the Brigham hospital.

Dr. Cohn published more than 500 peer-reviewed publications, 105 book chapters, and 12 books, including four editions of "Cardiac Surgery in the Adult." CHEST extends its heartfelt condolences to the entire Cohn family.



Dr. Cohn

# NUCALA

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

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

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



### Important Safety Information

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

##### Hypersensitivity Reactions

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

##### Acute Asthma Symptoms or Deteriorating Disease

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

##### Opportunistic Infections: Herpes Zoster

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

##### Reduction of Corticosteroid Dosage

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

##### Parasitic (Helminth) Infection

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

#### ADVERSE REACTIONS

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

## NUCALA IS PROVEN TO:

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

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

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

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

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

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Visit [NUCALAhcp.com](http://NUCALAhcp.com) for more information, including patient access programs.

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### Important Safety Information (cont'd)

#### ADVERSE REACTIONS (cont'd)

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

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

#### USE IN SPECIFIC POPULATIONS

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

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

Reference: 1. Data on file, GSK.

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

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**Nucala**<sup>®</sup>  
**(mepolizumab)**  
for Subcutaneous Injection  
100 mg/vial

## BRIEF SUMMARY

### NUCALA®

#### (mepolizumab) for injection, for subcutaneous use

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

#### INDICATIONS AND USAGE

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

#### Limitations of Use

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

##### Hypersensitivity Reactions

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

##### Acute Asthma Symptoms or Deteriorating Disease

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

##### Opportunistic Infections: Herpes Zoster

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

##### Reduction of Corticosteroid Dosage

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

##### Parasitic (Helminth) Infection

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

#### ADVERSE REACTIONS

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

- Hypersensitivity reactions [see Warnings and Precautions]
- Opportunistic infections: herpes zoster [see Warnings and Precautions]

#### Clinical Trials Experience

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

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

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

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

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

#### 52-Week Trial

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

#### Systemic Reactions, including Hypersensitivity Reactions

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

#### Injection Site Reactions

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

#### Long-Term Safety

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

#### Immunogenicity

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

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

#### DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

#### USE IN SPECIFIC POPULATIONS

##### Pregnancy

##### Pregnancy Exposure Registry

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

##### Risk Summary

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

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

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

#### Clinical Considerations

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

#### Data

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

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

#### **Lactation**

##### Risk Summary

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

##### **Pediatric Use**

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

##### **Geriatric Use**

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

##### **OVERDOSAGE**

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

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

##### **NONCLINICAL TOXICOLOGY**

###### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

##### **PATIENT COUNSELING INFORMATION**

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

##### Hypersensitivity Reactions

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

##### Not for Acute Symptoms or Deteriorating Disease

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

##### Opportunistic Infections: Herpes Zoster

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

##### Reduction of Corticosteroid Dosage

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

##### Pregnancy Exposure Registry

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

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# The changing face of MOC

BY HEATHER DETHLOFF, MA

CHEST Education and Accreditation Specialist

DR. KEVIN M. CHAN, FCCP

CHEST Representative to ABIM Liaison Committee on Certification and Recertification (LCCR), ABIM Pulmonary Board Member

**O**n April 8, 2106, CHEST joined 29 other medical specialty societies at the American Board of Internal Medicine's (ABIM's) biannual Liaison Committee on Certification and Recertification (LCCR) meeting in Philadelphia. The meeting focused on the changing face of Maintenance of Certification (MOC) and the vision ABIM has for the future of MOC.

President Dr. Richard J. Baron, responded to a letter signed by several medical specialty societies, asking for clarification on ABIM's vision and philosophy for MOC and the future changes ABIM is considering for the MOC program. Dr. Baron articulated the desire for MOC to be relevant to physicians' practices in collaboration with the ABIM and the medical specialty societies, to produce, "a credential that speaks to whether physicians are staying current in knowledge and practice over the course of their career in their specialty."

Dr. Richard G. Battaglia, ABIM Chief Medical Officer, and Eric McKeeby, ABIM Director of Community Engagement, reported the results of a membership survey and focus group discussions regarding ABIM's Assessment 2020 Report, published in September 2015. They highlighted

the challenges, opportunities, and future plans for the MOC program, in light of diplomates' input through these mechanisms. In the feedback received, the majority of diplomates favored a move away from the secure 10-year MOC recertification examination. Several options were presented, including smaller, more frequent exams, secure exams taken from home or office, and the ability to "test out" of the 10-year exam by successfully completing smaller assessments along the way. Ultimately, participants favored a move away from assessment and toward learning and improvement through a mechanism that is relevant to their real-world practices. Dr. Baron noted the ABIM survey results in which 76.3% of diplomates said they wanted the MOC credential to mean "I am staying current in the knowledge I need to practice," and he reiterated the Board's commitment to developing assessment approaches that would result in a meaningful credential based on performance. The ABIM Board of Directors met in April, with the exam format being a priority for them.

Regarding the future of MOC, while the practice assessment requirement is on hold through 2018, ABIM recognizes the work in this area many physicians are currently doing. By early 2017, ABIM is planning on extending the partnership with AC-CME to recognize practice assessment activities, along with current medical knowledge activities, for both CME and MOC. This expansion would include blended activities that meet both medical knowledge and practice assessment requirements.

In addition to ABIM staff's perspectives, three medical societies, including CHEST, reported on their MOC efforts. Heather Dethloff, CHEST Education and Accreditation Specialist, participated in a panel discussion, along with the Endocrine Society and the American Academy of Hospice and Palliative Medicine regarding the ongoing efforts to incorporate MOC into educational activities within their organizations. Successes and challenges encountered through the ABIM MOC certification process were the topics for discussion. During this presentation, CHEST announced its plan to incorporate ABIM MOC into the entire CHEST Annual Meeting 2016; details will be communicated to CHEST members and meeting registrants in coming months.

Throughout these changes to the MOC program, CHEST has been, and will continue to be, in communication with ABIM, advocating for our members. Any questions or concerns about this process can be directed to Heather Dethloff, Education and Accreditation Specialist, at [hdethloff@chestnet.org](mailto:hdethloff@chestnet.org).

## More information

New ABIM Survey Indicates Physician Interest in Potential Changes to MOC Assessment: [www.abim.org/news/new-abim-survey-indicates-physician-interest-in-potential-changes-to-moc-assessment.aspx](http://www.abim.org/news/new-abim-survey-indicates-physician-interest-in-potential-changes-to-moc-assessment.aspx)

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# Bedside test proves accurate across flu seasons

BY MARY ANN MOON  
Frontline Medical News

**A** rapid bedside diagnostic test for influenza showed consistent sensitivity and specificity across four consecutive flu seasons in a single pediatric ED in France, according to a report in *Diagnostic Microbiology and Infectious Disease*.

During flu seasons, it is difficult to distinguish young children who have the flu from those who have serious bacterial infections because clinical symptoms alone cannot differentiate the two conditions and fever may be the only symptom during the onset of a bacterial infection.

Rapid influenza diagnostic tests purport to help ED clinicians estimate the probability of influenza at the bedside, which in turn can reduce the need for further diagnostic test-

**These findings 'support the rational use of rapid influenza diagnostic tests in clinical practice for young children presenting with fever without a source during flu season.'**

ing, length of ED stay, inappropriate use of antibiotics, and the costs of care, said Dr. E. Avril of the pediatric ED, University Hospital in Nantes, France, and associates.

To assess the diagnostic value of one rapid influenza diagnostic test used in this setting every winter, the investigators studied 764 patients younger than age 5 years who were admitted to the ED during four consecutive flu seasons with fever of no known origin. The prevalence of influenza varied widely during the

study period, from a low of 30% to a high of 62%.

The rapid diagnostic test performed comparably well across the four flu seasons, with only a modest decrease in sensitivity and specificity during the

2010 H<sub>1</sub>N<sub>1</sub> flu pandemic. The bedside test had an overall sensitivity of 0.82, a specificity of 0.98, a positive likelihood ratio of 37.8, and a negative likelihood ratio of 0.19. These results are similar to those of two previous small-scale

studies that found sensitivities of 69%-85% and specificities of 83%-98%, Dr. Avril and associates said (*Diag Microbiol Infect Dis*. 2016 doi:10.1016/j.diagmicrobio.2016.03.015).

*Continued on following page*

OFEV IS RECOMMENDED\* FOR THE TREATMENT OF IPF BY THE ATS/ERS/JRS/ALAT GUIDELINES<sup>1</sup>

## SLOW THE PATH OF IPF PROGRESSION

OFEV (nintedanib) has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials<sup>2</sup>

OFEV significantly reduced the risk of first acute IPF exacerbation over 52 weeks compared with placebo in 2 out of 3 clinical trials<sup>2</sup>

Learn more about OFEV inside.

### INDICATION AND USAGE

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

### IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

#### Elevated Liver Enzymes

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

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

\*This conditional recommendation means that clinicians are encouraged to discuss preferences with their patients when making treatment decisions as the majority of patients would want treatment, but many would not.<sup>1</sup>

ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; ERS, European Respiratory Society; FVC, forced vital capacity; JRS, Japanese Respiratory Society.

 **OFEV**<sup>®</sup>  
(nintedanib)  
capsules 150mg

TREAT NOW. SLOW PROGRESSION.

### VIEW ON THE NEWS

**Dr. Susan Millard, FCCP, comments:** Avril and colleagues did a great job looking at a common problem with a large population studied over a long period of time! Fevers in children under 5 years of age can be anxiety provoking and costly to evaluate. This is great news about the specificity and sensitivity of this bedside flu test.



Continued from previous page

These findings “support the rational use of rapid influenza diagnostic tests in clinical practice for young children presenting with fever without a source during flu season,” the investigators said.

Dr. Avril and associates added that

they assessed only one rapid diagnostic test for influenza (QuickVue) – the only one available in their ED because of cost – but that there are 22 such tests commercially available. Nantes University Hospital supported the study.

Dr. Avril and associates reported having no relevant disclosures.



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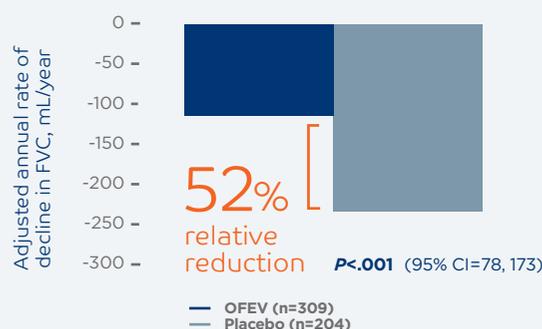
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## The totality of the evidence demonstrates that OFEV slows IPF progression<sup>2-6</sup>

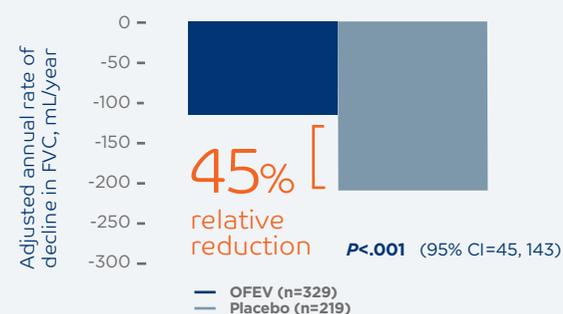
### REPRODUCIBLE REDUCTIONS IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 TRIALS<sup>2\*</sup>

#### INPULSIS<sup>®</sup>-1 (Study 2)<sup>2,7</sup>



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

#### INPULSIS<sup>®</sup>-2 (Study 3)<sup>2,7</sup>



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

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

CI, confidence interval; HR, hazard ratio.

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

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

### Gastrointestinal Disorders

#### Diarrhea

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

#### Nausea and Vomiting

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

# Immunization safe for preterm infants with BPD

BY WILLIAM PERLMAN  
Frontline Medical News

**D**espite concerns that preterm infants with bronchopulmonary dysplasia (BPD) are more likely

to experience respiratory decompensation after immunization than those without BPD, no difference in the incidence of respiratory decompensation within 72 hours after immunization was found between these groups

in a cohort study at a tertiary care facility, according to a report published April 11 in *Pediatrics*.

These results demonstrate the safety of immunizing preterm infants with BPD, and that the findings should ne-

gate delays in immunizations in these patients based on safety concerns described in previous studies, Dr. Edwin Clark Montague of Emory University, Atlanta, and his colleagues assert.

*Continued on following page*

## SIGNIFICANT REDUCTION IN THE RISK OF FIRST ACUTE IPF EXACERBATION OVER 52 WEEKS COMPARED WITH PLACEBO IN 2 OUT OF 3 CLINICAL TRIALS<sup>2</sup>

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

## THE MOST COMMON ADVERSE EVENTS WERE GASTROINTESTINAL IN NATURE AND GENERALLY OF MILD OR MODERATE INTENSITY<sup>2</sup>

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



ONE CAPSULE,  
TWICE DAILY WITH FOOD<sup>2</sup>

Not shown at actual size

Visit [hcp.OFEV.com](http://hcp.OFEV.com) for more information.

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

**Embryofetal Toxicity:** OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential hazard to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

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

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

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

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

 **OFEV<sup>®</sup>**  
(nintedanib)  
capsules 150mg

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Continued from previous page

In a retrospective observational study, Dr. Clark and his associates assessed a cohort of infants admitted to the NICU at a level 4, nonbirthing referral hospital, Children's Healthcare of Atlanta at Egleston, who received any immunizations while hospital-

ized between Jan. 1, 2008, and Aug. 1, 2014. Inclusion criteria were birth at less than 32 weeks' estimated gestational age and the availability of data for 72 hours before and 72 hours after immunization. The incidence of respiratory decompensation and cardiorespiratory events (apnea, bradycardia, desaturations) after im-

munization was compared between infants with and without BPD after immunization. (Pediatrics. 2016 doi: 10.1542/peds.2015-4225).

Of the 403 patients assessed, 240 met the inclusion criteria. Of these, 170 were identified as having BPD and were compared with the 70 patients without BPD. The study results

revealed no statistically significant difference in respiratory decompensation between patients with and without BPD. In addition, both groups showed an increased incidence of cardiorespiratory events, but there was no statistically significant difference between those with and without BPD.

In addition to BPD, the authors as-

GRANTED BREAKTHROUGH THERAPY DESIGNATION FOR IPF DURING FDA REVIEW<sup>9</sup>

## Start your appropriate patients with IPF on OFEV



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



**COMPLETE** the OFEV Prescription Form—available at [www.hcp.OFEV.com](http://www.hcp.OFEV.com)—and fax it to one of the participating specialty pharmacies listed on the form



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

### IMPORTANT SAFETY INFORMATION ADVERSE REACTIONS

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

### DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require

interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

### USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

OFHCPISISEP15

Please see brief summary for OFEV on the following pages.

**References:** 1. Raghu G et al; on behalf of the ATS, ERS, JRS, and ALAT. *Am J Respir Crit Care Med.* 2015;192(2):238-248. 2. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. 3. Zappala CJ et al. *Eur Respir J.* 2010;35(4):830-836. 4. Schmidt SL et al. *Chest.* 2014;145(3):579-585. 5. du Bois RM et al. *Am J Respir Crit Care Med.* 2011;184(12):1382-1389. 6. Song JW et al. *Eur Respir J.* 2011;37(2):356-363. 7. Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med.* 2014;370(22):2071-2082. 8. Richeldi L et al. *N Engl J Med.* 2011;365(12):1079-1087. 9. US Food and Drug Administration. [http://www.fda.gov/downloads/Regulatory Information/Legislation/FederalFoodDrugandCosmeticActFD-CAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM380724.pdf](http://www.fda.gov/downloads/Regulatory%20Information/Legislation/FederalFoodDrugandCosmeticActFD-CAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM380724.pdf). Accessed September 1, 2015.



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sessed risk factors that may predispose preterm infants to respiratory decompensation after immunization, such as a history of necrotizing enterocolitis or spontaneous intestinal perforation, grade III or IV intraventricular hemorrhage, or periventricular leukomalacia. Results from these analyses indicated that severe intraventricular hemorrhage was a predictor of respiratory decompensation after immunization, and that a

positive blood culture within 72 hours of immunization was predictive as well. The authors said that decompensation was likely secondary to the underlying infection in those with positive blood cultures, but that additional research would be required to better understand this finding.

The authors reported no external funding sources and no financial relationships relevant to this article.

## OFEV® (nintedanib) capsules, for oral use

### BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes:** The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment [see Use in Specific Populations]. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN [see Use in Specific Populations]. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders: Diarrhea:** Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the

reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV (nintedanib). **Nausea and Vomiting:** Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively [see Adverse Reactions]. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetotoxic in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV [see Use in Specific Populations]. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

**ADVERSE REACTIONS:** The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations [see Warnings and Precautions]; Gastrointestinal Disorders [see Warnings and Precautions]; Embryofetal Toxicity [see Warnings and Precautions]; Arterial Thromboembolic Events [see Warnings and Precautions]; Risk of Bleeding [see Warnings and Precautions]; Gastrointestinal Perforation [see Warnings and Precautions]. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to

89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV (nintedanib), more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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

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

<sup>a</sup> Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

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

<sup>c</sup> Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

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

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

## VIEW ON THE NEWS

**Dr. Susan Millard, FCCP, comments:** It is hard for me to understand why this is still controversial for pediatricians and family physicians. It is great that we have another study to show that infants with bronchopulmonary dysplasia can safely be immunized in a timely fashion.

# Score stratifies isolated tricuspid valve repair risk

BY MITCHEL L. ZOLER  
Frontline Medical News

PHOENIX – A team of cardiac surgeons has developed the first clinical risk score for predicting the risk that

patients face for operative mortality and postsurgical major morbidity when undergoing isolated tricuspid valve repair or replacement.

The risk score uses nine easily collected variables, and the derived

model discriminates outcomes based on patients who score from 0-10 or more points on both a mortality and a morbidity risk scale, Dr. Damien J. LaPar said at the annual meeting of the Society of Thoracic Surgeons.

The risk scores allow surgeons to better describe and quantify to patients considering isolated tricuspid valve surgery the risks they face from the operation, and they have already been incorporated into practice at the University of Virginia, in Charlottesville, where Dr. LaPar practices.

“Patients love to better understand their risks. We can provide them with empirical data from a large, heterogeneous population that are better than a surgeon’s gut feeling” about the risks they face, said Dr. LaPar, a cardiothoracic surgeon at the University.

Another consequence of having the new risk model and score is that it identified certain key risk factors that are controllable, and thereby, “makes the case for early referrals” for isolated tricuspid valve surgery, Dr. LaPar said in an interview. For example, the risk score shows that patients who are older, on hemodialysis, have a reduced left ventricular ejection fraction, or require emergency intervention all contribute to worse outcomes, compared with patients who are younger, have better renal function, better cardiac output, or can be treated on a more routine basis.

Many physicians have viewed isolated tricuspid valve surgery as posing similar risks to all patients, with an overall average operative mortality rate of about 10%, he noted. The new risk score model shows that some patients who are younger and healthier have operative mortality rates below 5%, while older and sicker patients have rates that can surpass 20%.

“Our data show a spectrum of risk, and that it is better to operate sooner than later. That is the huge clinical message of these data,” Dr. LaPar said.

Designated discussant Dr. Michael A. Acker noted that the risk score for

*Continued on following page*

anticoagulation treatment as necessary [see *Warnings and Precautions*].

**USE IN SPECIFIC POPULATIONS: Pregnancy:** *Pregnancy Category D.* [See *Warnings and Precautions*]: OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed

between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see *Warnings and Precautions*]. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

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

**PATIENT COUNSELING INFORMATION:** Advise the patient to read the FDA-approved patient labeling (*Patient Information*). **Liver Enzyme and Bilirubin Elevations:** Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [see *Warnings and Precautions*]. **Gastrointestinal Disorders:** Inform patients that gastrointestinal disorders such as diarrhea, nausea,

and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see *Warnings and Precautions and Adverse Reactions*]. **Pregnancy:** Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV [see *Warnings and Precautions and Use in Specific Populations*]. **Arterial Thromboembolic Events:** Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see *Warnings and Precautions*]. **Risk of Bleeding:** Bleeding events have been reported. Advise patients to report unusual bleeding [see *Warnings and Precautions*]. **Gastrointestinal Perforation:** Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see *Warnings and Precautions*]. **Nursing Mothers:** Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing [see *Use in Specific Populations*]. **Smokers:** Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. **Administration:** Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see *Dosage and Administration*].

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## VIEW ON THE NEWS

**Dr. Hossein Almassi, FCCP, comments:** Historically, isolated tricuspid valve repair has been associated with a high mortality rate.

The report from the University of Virginia is an attempt in the right direction for risk stratifying the patients preoperatively, therefore, assisting cardiologists and cardiac surgeons in devising a timely plan of appropriate therapy for their patients.

# Post-MVR regurgitation may be worse than thought

BY RICHARD MARK KIRKNER  
*Frontline Medical News*

In patients who undergo transcatheter mitral valve repair for mitral valve regurgitation (MR), residual mild (+2) regurgitation has been considered procedural success, but a team of Italian investigators has provided evidence that such a result may actually foretell far worse long-term outcomes than residual trace ( $\leq 1$ ) MR.

The investigators from San Raffaele Scientific Institute in Milan reported their findings in the *Journal of Thoracic and Cardiovascular Surgery* (J Thorac Cardiovasc Surg 2016;151:88-96). They compared follow-up outcomes of 223 consecutive patients with residual MR 2+ and MR  $\leq 1$  after implantation of the MitraClip system (Abbott Vascular). The procedures were performed between October 2008 and December 2014.

"In this study we found a clear unfavorable impact on follow-up outcomes of acute residual 2+ MR after MitraClip repair when compared to residual  $\leq 1$  MR," lead author Dr. Nicola Buzzatti and colleagues said.

The study cited a scarcity of data on the long-term impact of residual mild MR. "This topic is therefore par-

ticularly of interest, especially when assessing the convenience to expand transcatheter mitral repair procedures to intermediate or low-risk patients," Dr. Buzzatti and coauthors said.

The study group all had moderate or greater ( $\geq 3$ ) MR when they underwent mitral valve repair (MVR). The post-MVR study cohort excluded patients who had residual MR of 3 or greater, which was considered a procedural failure. Four patients died within 30 days, each from a different cause: multi-organ failure, lung rupture, pneumonia with heart failure, and sudden death. The overall 30-day death rate was 1.8%.

**'The probability of failure of recurrence of moderate or severe MR with residual MR  $\leq 1$  was 5.6% at 24 months and 13.3% at 48 months.' Comparatively, with residual MR 2+, it was 45.2% at both 24 and 48 months.'**

Among the remainder of patients, the average follow-up was 20.5 months, with some follow-up extending to 75 months. The overall survival was 74.4% at 24 months and 63% at 48 months.

The study calculated the cumulative incidence function, or the probability of failure, of cardiac death in patients with residual MR  $\leq 1$  at 7.1% at 24 months and 10.9% at 48 months, compared with 26.9% at 24 months and 35.3% at 48 months in those with MR 2+. The probability of failure of recurrence of moderate or severe MR with residual MR  $\leq 1$

## VIEW ON THE NEWS

**Dr. Hossein Almassi, FCCP, comments:** Transcatheter mitral valve repair using MitraClip in high-risk patients has gained popularity; however, as indicated in this report from Milan, Italy, the success rate of the procedure as defined by the presence of 2+ MR or less should be taken with great caution. The Milan Center is where the concept of surgical edge-to-edge repair of the mitral valve; the so-called Alfieri repair, was developed. In the surgical repair of mitral valve the presence of 2+ MR in the operating

room mandates the reopening of the left atrium and the revision of repair. This report and the accompanying editorial reinforces the time tested principle that the presence of residual MR of 2+, especially in functional MR, is associated with worse survival, symptom relief, and progression to more severe MR. The report should be a cautionary note to the implanting centers of MitraClip to not expand the indications to lower risk patients before the efficacy of this technology is improved.

was 5.6% at 24 months and 13.3% at 48 months, compared with 45.2% at both 24 and 48 months with residual MR 2+. "The difference between MR  $\leq 1$  and MR=2 was significant," Dr. Buzzatti and colleagues said.

The researchers separately evaluated outcomes among those who had functional MR (FMR) and degenerative MR (DMR). In FMR, patients with MR 2+ had a higher risk profile at baseline because of a slightly higher rate of advanced heart disease; they typically had larger ventricles with larger mitral valves and greater pulmonary pressure than the  $\leq 1$  MR patients. "Notably, these features could have impaired the surgeon's ability to achieve acute optimal MR reduction during the MitraClip procedure," Dr. Buzzatti and coauthors said. "For sure, advanced left ventricle

remodeling was a strong independent predictor of increased cardiac death." The study authors could not draw a similar conclusion with DMR because only three patients in the group died of cardiac causes.

MR recurrence was "remarkably higher" in MR 2+ patients, compared with the MR  $\leq 1$  group with FMR and DMR, and MR 2+ developed in 21.4% of the FMR group within 30 days of the procedure. "This poor efficacy results in a population of patients who were supposed to have had a 'procedural success' is striking," Dr. Buzzatti and coauthors noted.

Dr. Buzzatti and coauthor Dr. Paolo Denti disclosed receiving consultant fees from Abbott Vascular. Coauthor Dr. Fabio Barili disclosed receiving consultant fees from St. Jude Medical. The other coauthors had no relationships to disclose.

*Continued from previous page*

tricuspid-valve surgery "is a first of its kind and a major contribution." Dr. Acker is professor of surgery and chief of cardiovascular surgery at the University of Pennsylvania in Philadelphia. He is a consultant to Thoratec and HeartWare.

Dr. LaPar and his associates derived the risk model and score from data collected on 2,050 patients who underwent isolated tricuspid valve repair or replacement at 49 hospitals in Virginia or Michigan during 2002-2014. The data came from databases maintained by the Virginia Cardiac Surgery Quality Initiative and by the Michigan Society of Thoracic & Cardiovascular Surgeons, and reported to the Adult Cardiac Surgery Database of the Society of Thoracic Surgeons. The model they developed showed operative mortality rates that ranged from 2%, for patients with a mortality score of zero, to 34% for patients with a score of 10 or more. It further showed major morbidity rates of 13%, for patients with a morbidity score of zero, to 71% for those with a score of 10 or



Dr. Damien J. LaPar

more. Scoring for mortality uses a slightly different system than the scoring for morbidity, so the scores must be calculated individually, and the score totals for a patient can differ for each endpoint. The maximum score is 22 for mortality and 23 for morbidity.

Only 5%-15% of patients undergoing tricuspid valve surgery have an isolated procedure, so a relatively limited number of patients fall into this category, a fact that has in the past limited collection of data from large numbers of patients. The dataset used for this analysis, with 2,050 patients "is one of the largest series collected," and made possible derivation of a robust risk model and scoring system. Future analysis of even more patients should further improve the model and scoring system.

"These data set the stage for looking at national-level data to further refine the model and make it even more generalizable," Dr. LaPar said.

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# Wanted: Better evidence on fast-track lung resection

BY RICHARD MARK KIRKNER  
*Frontline Medical News*

**A** host of medical specialties have adopted fast-track or enhanced-re-

covery pathways to speed recovery of surgical patients, reduce length of hospital stays, and cut costs. But when it comes to elective lung resection, the medical evidence has yet to establish if patients in expedited

recovery protocols fare any better than do those in a conventional recovery course, a systematic review in the *Journal of Thoracic and Cardiovascular Surgery* reported (2016 Mar;151:708-15).

Investigators from McGill University in Montreal performed a systematic review of six studies that evaluated patient outcomes of both traditional and enhanced-recovery pathways (ERPs) in elective lung resection. They concluded

## VIEW ON THE NEWS

### ERPs may be hard to replicate

**T**he task that Dr. Fiore and colleagues undertook to evaluate and compare disparate studies of fast-track surgery in lung resection is akin to comparing not just apples and oranges but apples and zucchini.

Without the authors' descriptive approach, the results of a true meta-analysis would be uninterpretable.

Nonetheless, the systematic review underscores the need for a blinded, randomized trial. Furthermore, rather than measuring hospital stay, subjects should be evaluated for readiness for discharge, because this would reduce the effect of systems-based obstacles to discharge.

Enhanced recovery pathways in colorectal surgery have been used as models for other specialties, but the novelty of these pathways versus traditional care may be difficult to replicate in thoracic surgery. Strategies such as antibiotic prophylaxis and epidural analgesia in thoracic surgery are not dissimilar enough from standard care to elicit a difference in outcome.

In thoracic surgery, enhanced recovery pathways must consider the challenges of pain control and chest tube management unique in these patients.

For pain control, paravertebral blockade rather than epidural analgesia could lead to earlier hospital discharges.

Use of chest tubes is commonly a matter of surgeon preference, but chest tubes without an air leak and with acceptable fluid output can be safely removed, and even patients with an air leak but no pneumothorax on water seal can go home with a chest tube.

*Dr. Lisa M. Brown of the University of California, Davis, Medical Center made these remarks in her invited analysis (J. Thorac. Cardiovasc. Surg. 2016 Mar;151:715-16) Dr. Brown had no financial relationships to disclose.*

- ▶ In two observational studies, 33% to 67% of patients using pMDIs\* had poor hand-breath coordination during inhalation<sup>1,2</sup>
- ▶ A spacer is intended to help with pMDI use, but you or your patients may be looking for an option that doesn't rely on a separate device to help<sup>3</sup>
- ▶ A breath-actuated inhaler, like ProAir® RespiClick (albuterol sulfate) Inhalation Powder, is an option to consider for these patients

### Indications

ProAir® RespiClick (albuterol sulfate) Inhalation Powder is indicated in patients 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

### Important Safety Information

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



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that ERPs may reduce the length of hospital stays and hospital costs but that well-designed trials are needed to overcome limitations of existing studies.

“The influence of ERPs on postoperative outcomes after lung resection has not been extensively studied in comparative studies involving a control group receiving traditional care,”

lead author Julio F. Fiore Jr., Ph.D., and his colleagues said. One of the six studies they reviewed was a randomized clinical trial. The six studies involved a total of 1,612 participants (821 ERP, 791 control).

The researchers also reported that the studies they analyzed shared a significant limitation. “Risk of bias

favoring enhanced-recovery pathways was high,” Dr. Fiore and his colleagues wrote. The studies were unclear if patient selection may have factored into the results.

Five studies reported shorter hospital length of stay for the ERP group. “The majority of the studies reported that LOS was significantly shorter when

patients undergoing lung resection were treated within an ERP, which corroborates the results observed in other surgical populations,” Dr. Fiore and his colleagues said.

Three nonrandomized studies also evaluated costs per patient. Two reported significantly lower costs for

*Continued on following page*

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  - A breath-actuated inhaler designed to be used without a spacer<sup>4</sup>
- Transition your appropriate patients from a pMDI SABA inhaler to

### ProAir® RespiClick (albuterol sulfate) Inhalation Powder

Learn more at [ProAir.com](http://ProAir.com)



#### Important Safety Information (continued)

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

Please see Brief Summary of full Prescribing Information on following pages.

\* pMDI=pressurized metered-dose inhaler.

† SABA=short-acting beta agonist.

**References:** 1. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J.* 2002;19(2):246-251. 2. Khassawneh BY, Al-Ali MK, Alzoubi KH, et al. Handling of inhaler devices in actual pulmonary practice: metered-dose inhaler versus dry powder inhalers. *Resp Care.* 2008;53(3):324-328. 3. National Asthma Education and Prevention Program (NAEPP). *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma—Full Report 2007.* Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; August 2007. 4. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005;127(1):335-371.

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ERP patients: \$13,093 vs. \$14,439 for controls; and \$13,432 vs. \$17,103 for controls (Jpn. J. Thorac. Cardiovasc. Surg. 2006 Sep;54:387-90; Ann. Thorac. Surg. 1998 Sep;66:914-9). The third showed what the authors said was no statistically significant

cost differential between the two groups: \$14,792 for ERP vs. \$16,063 for controls (Ann. Thorac. Surg. 1997 Aug;64:299-302).

Three studies evaluated readmission rates, but only one showed measurably lower rates for the ERP group: 3% vs. 10% for controls (Lung Cancer. 2012 Dec;78:270-5).

Three studies measured complication rates in both groups. Two reported cardiopulmonary complication rates of 18% and 17% in the ERP group vs. 16% and 14% in the control group, respectively (Eur. J. Cardiothorac. Surg. 2012 May;41:1083-7; Lung Cancer. 2012 Dec;78:270-5). One reported rates of pulmonary com-

plications of 7% for ERP vs. 36% for controls (Eur. J. Cardiothorac. Surg. 2008 Jul;34:174-80).

The researchers acknowledged that studies involving other surgical specialties have validated the role of ERP, along with minimally invasive surgery, to improve outcomes. They disclosed no financial relationships.

#### BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR ProAir® RespiClick (albuterol sulfate) Inhalation Powder

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

#### 1 INDICATIONS AND USAGE

##### 1.1 Bronchospasm

PROAIR RESPICLICK (albuterol sulfate) inhalation powder is indicated for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease.

##### 1.2 Exercise-Induced Bronchospasm

PROAIR RESPICLICK is indicated for the prevention of exercise-induced bronchospasm in patients 12 years of age and older.

#### 4 CONTRAINDICATIONS

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

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Paradoxical Bronchospasm

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

##### 5.2 Deterioration of Asthma

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

##### 5.3 Use of Anti-Inflammatory Agents

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

##### 5.4 Cardiovascular Effects

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

##### 5.5 Do Not Exceed Recommended Dose

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

##### 5.6 Immediate Hypersensitivity Reactions

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

##### 5.7 Coexisting Conditions

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

##### 5.8 Hypokalemia

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

#### 6 ADVERSE REACTIONS

Use of PROAIR RESPICLICK may be associated with the following:

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

#### ProAir® RespiClick (albuterol sulfate) Inhalation Powder

##### 6.1 Clinical Trials Experience

A total of 1120 subjects were treated with PROAIR RESPICLICK during the clinical development program. The most common adverse reactions ( $\geq 1\%$  and  $>$ placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

**Table 1: Adverse Reactions Experienced by Greater Than or Equal to 1.0% of Patients in the PROAIR RESPICLICK Group and Greater Than Placebo in three 12-Week Clinical Trials<sup>1</sup>**

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

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

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

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

##### 6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with PROAIR RESPICLICK, the following adverse events have been reported during use of other inhaled albuterol sulfate products: Urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (potentially fatal), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

#### 7 DRUG INTERACTIONS

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

##### 7.1 Beta Blockers

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

##### 7.2 Diuretics

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

##### 7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical signif-

# SLEEP STRATEGIES Treating childhood OSA

*Watchful waiting may be indicated for some children with OSA; however, there are no absolute guidelines yet on which children may avoid surgery.*

BY DR. JULIE BAUGHN

In most children, obstructive sleep apnea (OSA) is a curable disease that responds to surgical treatment with adenotonsillectomy. Do

all children need surgery for their sleep apnea? Recent research suggests perhaps not. Some children with mild obstructive sleep apnea may “grow out of it” without having their tonsils and adenoids removed.



DR. BAUGHN

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importance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR RESPICLICK.

### 7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Teratogenic Effects:** Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR RESPICLICK or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR RESPICLICK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m<sup>2</sup> basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD. In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD.

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

### 8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR RESPICLICK for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR RESPICLICK has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta<sub>2</sub>-agonists, including albuterol.

### 8.3 Nursing Mothers

Plasma levels of albuterol after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR RESPICLICK are excreted in human milk.

Caution should be exercised when PROAIR RESPICLICK is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR RESPICLICK by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of PROAIR RESPICLICK for the treatment or prevention of bronchospasm in children 12 to 17 years of age and older with reversible obstructive airway disease is based on two 12-week clinical trials in 318 patients 12 years of age and older with asthma comparing doses of 180 mcg four times

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

The safety and effectiveness of PROAIR RESPICLICK in pediatric patients below the age of 12 years have not been established. Overall, 120 children with asthma ages 4 to 11 years have participated in the PROAIR RESPICLICK clinical program, including 76 patients evaluated in 2 single-dose crossover clinical trials comparing PROAIR RESPICLICK to ProAir HFA at doses up to 180 mcg.

### 8.5 Geriatric Use

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

All beta<sub>2</sub>-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

## 10 OVERDOSAGE

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

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR RESPICLICK. Treatment consists of discontinuation of PROAIR RESPICLICK together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR RESPICLICK.

Respiratory

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This brief summary is based on the ProAir RespiClick full prescribing information dated March 2015.

PRS-40076 March 2015

## New research may identify children who can avoid surgery

The Childhood Adenotonsillectomy Trial (CHAT), first published in 2013, suggested to clinicians that a higher than realized number of children may grow out of their OSA (Marcus et al. *N Engl J Med.* 2013;368[25]:2366). This was the first study to examine the risks and benefits of early adenotonsillectomy vs. watchful waiting in children 5 to 9 years of age. When sleep studies were performed at baseline and at 7 months of follow-up, it was found that 46% of the children in the watchful waiting group had resolution of their OSA. In addition, it was noted that resolution of OSA after adenotonsillectomy was not absolute, either, as 21% in the early adenotonsillectomy group had residual OSA at 7 months postsurgery. This leads to the questions of which children should undergo surgery and how we are to identify them.

A more recent study by Chervin and colleagues published in *CHEST* identifies factors associated with resolution of sleep apnea in the children in the watchful waiting arm of the CHAT trial (*Chest.* 2015;148[5]:1204). The factors identified included baseline polysomnography characteristics of mild sleep apnea, such as lower baseline apnea/hypopnea index (AHI) and less oxygen desaturation. Figure 1 (see next page) demonstrates the percentage of children in the watchful waiting group who had resolution of their OSA by their baseline AHI.

The CHAT trial did not include many children with severe OSA, as median AHI was less than 5, and children with sustained desaturations were excluded. Chervin and colleagues noted that those children with a lower AHI and waist circumference profile were more likely to have resolution. Other factors that may also be associated with resolution without surgery suggested by these data include a lower waist

*Continued on following page*

Continued from previous page

circumference percentile and lower baseline questionnaire scores on the pediatric sleep questionnaire (PSQ). The PSQ has also been identified as a tool to help assess for likelihood of OSA. Some clinical factors may also be associated with resolution of OSA, such as the absence of loud or habitual snoring or observed apneas. The identification of these factors,

### A lower waist circumference percentile and lower baseline questionnaire scores on the pediatric sleep questionnaire are some factors that may be associated with resolution without surgery.

along with future research in pediatric OSA, may begin to help practitioners to identify children who can avoid surgery and help identify those who may have residual disease after surgery.

While AHI improved in a large portion of children in this study, symptoms did not show as drastic an

association. Only 15% had a symptomatic improvement in questionnaire scores of at least 25% (Chervin et al, previous mention).

Researchers are also examining biomarkers associated with OSA. A recent study showed that increased C-reactive protein (CRP) levels were associated with residual OSA after adenotonsillectomy (Bhattacharjee et al. *Sleep*. 2016;39[2]:283).

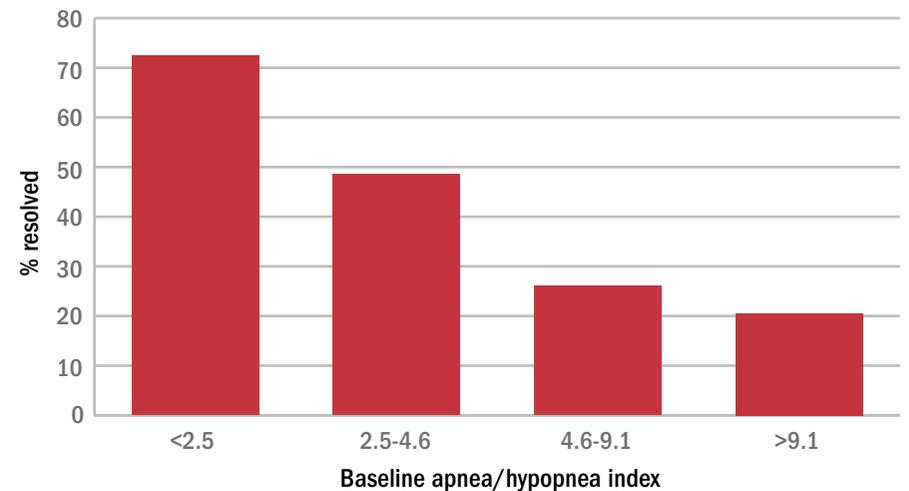
#### Why is this important?

OSA in children is common and affects an estimated 1% to 5% of children (Marcus et al. *Pediatrics*. 2012;130[3]:576). In the majority of children, this is due to hypertrophy of their tonsils and adenoids. Other factors, such as obesity, craniofacial features, and genetic syndromes, can play a role. Many studies examining the effects of OSA in children have demonstrated a negative impact on attention, cognitive function, and behavior. There is often significant impact on other members of a household when a child has a sleep disorder. Longitudinal effects on how OSA in childhood impacts adulthood are still unknown.

#### The impact of surgery

Approximately half a million adenotonsillectomies are per-

### OSA resolution after 7 months, by baseline AHI quartile



Note: The study involved 194 children aged 5-9 years.

Source: *Chest*. 2015;148(5):1204-13

formed per year in the United States, with the indication primarily due to OSA increasing from being primarily for infection during the past several decades (Bhattacharyya et al. *Otolaryngol Head Neck Surg*. 2010;143[5]:680).

Minor complications, such as throat pain and dehydration, are common. Primary (within 24 hours) and secondary (typically between 5 and 10 days postoperatively) bleeding can occur in 2% to 3% of children.

Respiratory compromise is a com-

plication that is an increased risk when the indication for surgery is OSA and can occur in almost 10% of children (De Luca Canto et al. *Pediatrics*. 2015;136[4]:702).

Cost of surgery and missed days of school (child) and work (parent) can all be factors.

The decision for surgery rests on the parents, and they may have varying preferences as to how aggressively they want their child to be treated with surgery. While surgery is often curative, it is not 100%.

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### How is obstructive sleep apnea diagnosed in children?

Obstructive sleep apnea is diagnosed by overnight sleep study or polysomnography. Criteria for diagnosis of OSA in children can vary in the literature, but criteria used clinically are often similar to what was used in the CHAT trial: an obstructive AHI greater than 2 per hour or an ob-

structive apnea index (OAI) of greater than one per hour. Alternatives to an overnight sleep study have not yet been found for children. In adults, overnight oximetry, if normal, can be valuable in ruling out obstructive sleep apnea. In children, almost 50% of those screened with a normal oximetry went on to have sleep apnea during an overnight sleep study, making this an ineffective screening tool to rule out sleep apnea for most children (Brouillette et al. *Pediatrics*. 2000;105[2]:405). Home sleep testing has yet to be shown to be a reliable option in

children but may be in the future (Tan et al. *Chest*;2015:148[6]:1382). Clinical history taking can be more challenging as well, as children do not typically have bed partners, and OSA is often clustered in the early morning hours in association with rapid eye movement sleep (REM), making parental observation less likely. These factors make overnight

sleep studies the gold standard for diagnosis. However, overnight sleep studies are costly, time consuming, and can be technically challenging in children depending on age and development. In certain areas, access to pediatric sleep centers can be limited. Overnight sleep studies can also be an economic burden to parents who are required to spend the night with their child, perhaps missing work and needing child care for other children in the family. All of this adds to the importance of identifying children who truly need to undergo a sleep study.

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### Can we change guidelines? Not yet.

We are not at a point where we can yet rewrite guidelines. The American Academy of Pediatrics (AAP) and the American Academy of Sleep Medicine (AASM) recommend a sleep study prior to proceeding to adenotonsillectomy in children. A repeat sleep study is recommended in children with moderate to severe OSA after adenotonsillectomy and when symptoms remain. Are there any other tools that can be used? New research may give suggestion as to which children can avoid repeating the costly and time-consuming test. In areas where sleep studies have limited availability, avoiding unnecessary testing is important.

### Bottom line: More questions remain

The diagnosis and treatment of childhood OSA continue to challenge practitioners. While adenotonsillectomy is still the common treatment for OSA, it is reasonable to consider watchful waiting in some circumstances, particularly in children with mild disease. More questions still remain, however, in regards to the follow-up of these children. Practitioners still struggle with the definition of mild OSA in children (Is this an AHI less than 3, or is this an

AHI less than 5? How do symptoms impact diagnosis and treatment?). Studies such as the CHAT trial are important first steps in helping to sort out the behavior of OSA. What happens to children farther out than 7 months? Additional research should help clarify these issues.

*Dr. Baughn is a Consultant, Pediatric Pulmonology and Sleep Medicine, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota.*

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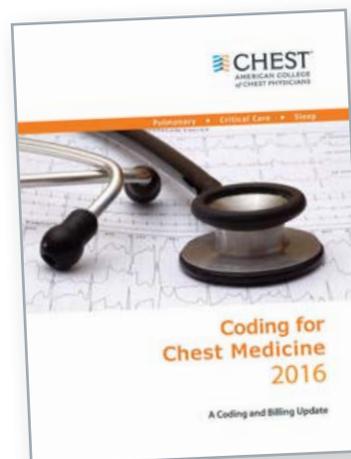
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# NETWORKS: Hospital violence, angioplasty for CTEPH, lung nodules

## Pulmonary Physiology, Function, and Rehabilitation

### Utility of the acute bronchodilator response

Recently, numerous articles evaluating the acute bronchodilator (BD) response in various disease states have appeared in the literature (*Chest*. 2015;148[6]:1489; *J Thorac Dis*. 2016;8[1]:14; *Int J Chron Obstruct Pulmon Dis*. 2016;11:93; *Respir Med*. 2016;112:45). New algorithms have been proposed to improve quality control in BD (*Eur Clin Respir J*. 2015;30:2). In our lab, requests for pre- and post-BD spirometry continue unabated. Undoubtedly, many labs comply with these requests without regard for pre-BD values. The number of these requests far exceeds the number needed to confirm asthma diagnosis, or to assure that post-BD FEV<sub>1</sub>/FVC ratio remains below 0.7 for COPD diagnosis, which are the only universally accepted indications for BD testing.



DR. HNATIUK

Acute BD testing technique, interpretation, and clinical application involve important issues that remain unresolved, even in COPD where this test has been studied more than any other disease state except asthma (*Chest*. 2011;140[4]:1055; *Int J Chron Obstruct Pulmon Dis*. 2015;10:407). There remains no clear consensus for a clinically relevant BD response. The ACCP definition proposed in 1974 (FEV<sub>1</sub> improvement by greater than 15%) has not been updated, and the widely used ATS/ERS definition (FEV<sub>1</sub> and/or FVC improvement by greater than 12% and 200 mL) is felt to be arbitrary and based more on expert opinion than scientific evidence (*Respir Care*. 2012;57[10]:1564).

Literature review (excluding asthma) reveals no well-done, reproducible studies that demonstrate meaningful or widely applicable uses for the acute BD response. Overcoming the many factors influencing acute bronchodilator testing, developing a unified definition for a positive test, and then showing a predictive significance to the acute-BD response is an extremely difficult task. Until this test is further studied in a rigorous manner, any meaning attached to a positive response outside of asthma is purely arbitrary.

Dr. Oleh Hnatiuk, FCCP  
Steering Committee Member

## Disaster Response

### Gun violence in the hospital

Thirty-one thousand fatal gunshot wounds (GSW) occur in the United States each year and are increasing; 55% are self-inflicted, mostly isolated incidents. However, mass shooting events (MSE = more than 3 victims) are rising with 355 events in 2015 (462 deaths and 1,314 injuries). The mortality of GSW has risen due to the use of high caliber automatic handguns. Health-care providers, facilities, and systems need to include preparation for primary prevention and secondary mitigation for violent acts of this nature. MSE attacker demographics reveal a male predominance (90%) with ethnicity mirroring the US population (65% Caucasian, 16% black, and 9% Asian) and mainly occurring in urban settings. The psychosocial basis of these changes is complex and multifactorial. Two-thirds of mass shooters have a history of mental

illness with paranoid schizophrenia predominating. Motives are shifting from self-destruction to grievance-related events. Targets and victims of GSW violence also seem to be changing, and health-care workers are potential targets for GSW violence.



DR. AMUNDSON

A 12-year review of hospital shooting events (HSE) found 154 events with 235 victims. There is a rise in this type of violent act. Grievance motives are dominant in these events. Most HSE occur in the ED or at the entrance to the hospital or parking lot (77%). The case fatality rate in HSE averages 50%. The perpetrators are injured in 85% of cases. Nurses are the most common victims of HSE.

Prevention strategies such as metal detectors, camera surveillance, strengthened security staff, and emergency protocols are vital. However, in many hospitals, these strategies are inadequate or not considered. Secondary mitigation requires special education and training and some material preparation to be successful. Providers must consider themselves potential gun violence victims. We encourage all medical providers to engage in planning and preparation for HSE, as well as advocate for gun safety laws

Dr. Dennis Amundson, FCCP  
NetWork Member

### References

- Critical violent injury in the United States: A review and call to action. *Crit Care Med*. 2015;43(11):2460-2466.
- Hospital-based shooting in the United States: 2000-2011. *Ann Emerg Med*. 2012;60(6):790-798.
- The epidemiology of trauma-related mortality in the United States From 2002-2012. *J Trauma Acute Care Surg*. 2014;76(4):913-920.

## Pulmonary Vascular Disease

### Balloon pulmonary angioplasty for CTEPH

The gold-standard treatment for chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary thromboendarterectomy (PTE). However, not every patient is a surgical candidate, including those who are deemed technically inoperable (after review by a multidisciplinary, experienced CTEPH team) or those whose goals of care are more palliative.

Such factors created an opportunity for an alternative procedure to manage CTEPH: catheter-based balloon pulmonary angioplasty (BPA). Despite the limited success with early BPA experience, with initial set-backs including high reperfusion edema rates and other procedure complications, BPA has become more refined over time. Initially led by the efforts of several groups based in Japan, modifications included greater precision in "right-sizing" balloons, staging the procedure (average two to five sessions/patient), and better vascular imaging techniques with advancing technical capabilities.

BPA has received attention due to the favorable hemodynamic and functional outcomes reported in select patients. Despite a lack of consensus regarding who might benefit most, these preliminary results have stimulated considerable interest for acquiring this technique worldwide.

Caution should be exercised when BPA is considered for CTEPH treatment. Critical to success is the

selection of patients who might benefit, and adequate training and technical expertise is essential for BPA performance. For those with operable CTEPH who are otherwise surgical candidates, data do not yet exist to suggest BPA as a comparable alternative to PTE. Furthermore, the absence of head-to-head comparison between medical therapy and BPA for inoperable CTEPH further blurs the role BPA will have in this unique patient population. But, it holds promise, awaiting further trials data.

Dr. Wassim H. Fares, FCCP  
NetWork Member  
Dr. William R. Auger, FCCP,  
Steering Committee Member

## Thoracic Oncology

### Pulmonary nodules: Are you seeing spots?

Pulmonary nodules are increasingly being identified in clinical practice. A recent study estimated that 1.5 million nodules are identified annually in the United States (Gould et al. *Am J Respir Crit Care Med*. 2015; 192[10]:1208). This 10-fold increase in number over prior estimates reflects the steep escalation in utilization of CT scanning over the past several decades, and is likely to rise further as lung cancer screening is implemented. While the majority of nodules are benign, evaluation necessarily includes an assessment of the probability of malignancy, since this is a major driver of the decision as to whether no further intervention is required, or whether watchful surveillance or further noninvasive or invasive evaluation is appropriate (Gould et al. *Chest*. 2013;143[5 suppl]:e93S).

It is reassuring that experienced chest physicians perform well in the assessment of the probability of malignancy (Gould et al, 2013; Swensen et al. *Mayo Clin Proc*. 1999;74[4]:319), but also important to recognize that evidence-based guidelines for nodule evaluation as well as validated tools for assessing the likelihood of malignancy are readily available (Gould et al. *Chest*. 2007;131[2]:383; Gould et al, 2013; McWilliams et al. *N Engl J Med*. 2013;369[10]:910; Swensen et al. *Arch Intern Med*. 1997;157[8]:849). It is important to engage our radiology colleagues in this discussion; guidelines from the Fleischner Society and the American College of Radiology for reporting on incidentally identified small solid nodules, incidentally identified subsolid nodules, and screening-detected nodules are individually distinct in definitions of abnormality as well as recommendations for follow up, and should be applied appropriately in the context of the individual patient as well as the situation for which the CT was performed (Lung-RADS Version 1.0 Assessment Categories Release date: April 28, 2014. <http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/LungRADS/AssessmentCategories.pdf>. Accessed Oct 31, 2014; MacMahon et al. *Radiology*. 2005;237[2]:395; Naidich et al. *Radiology*. 2013;266[1]:304). All of these potential sources of variation highlight the value of standardizing the approach to nodule evaluation, to ensure that appropriate evaluation will be done to maximize the likelihood of identifying nodules that are actually cancer, and minimize harm potentially incurred by unnecessary invasive and noninvasive testing of nodules that are actually benign.

Dr. Lynn Tanoue, FCCP  
NetWork Chair



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## BE IN THE

PAH (WHO Group 1) and CTEPH (WHO Group 4) are associated with impaired synthesis of nitric oxide (NO)



When your adult PAH and CTEPH patients aren't at goal  
**kNOw** why to check **YES** for **Adempas**



### INDICATIONS

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

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

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

Please see additional Important Safety Information, including Boxed Warning, inside and Brief Summary of Prescribing Information at end of advertisement.

### IMPORTANT SAFETY INFORMATION

#### WARNING: EMBRYO-FETAL TOXICITY

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

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

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



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riociguat tablets

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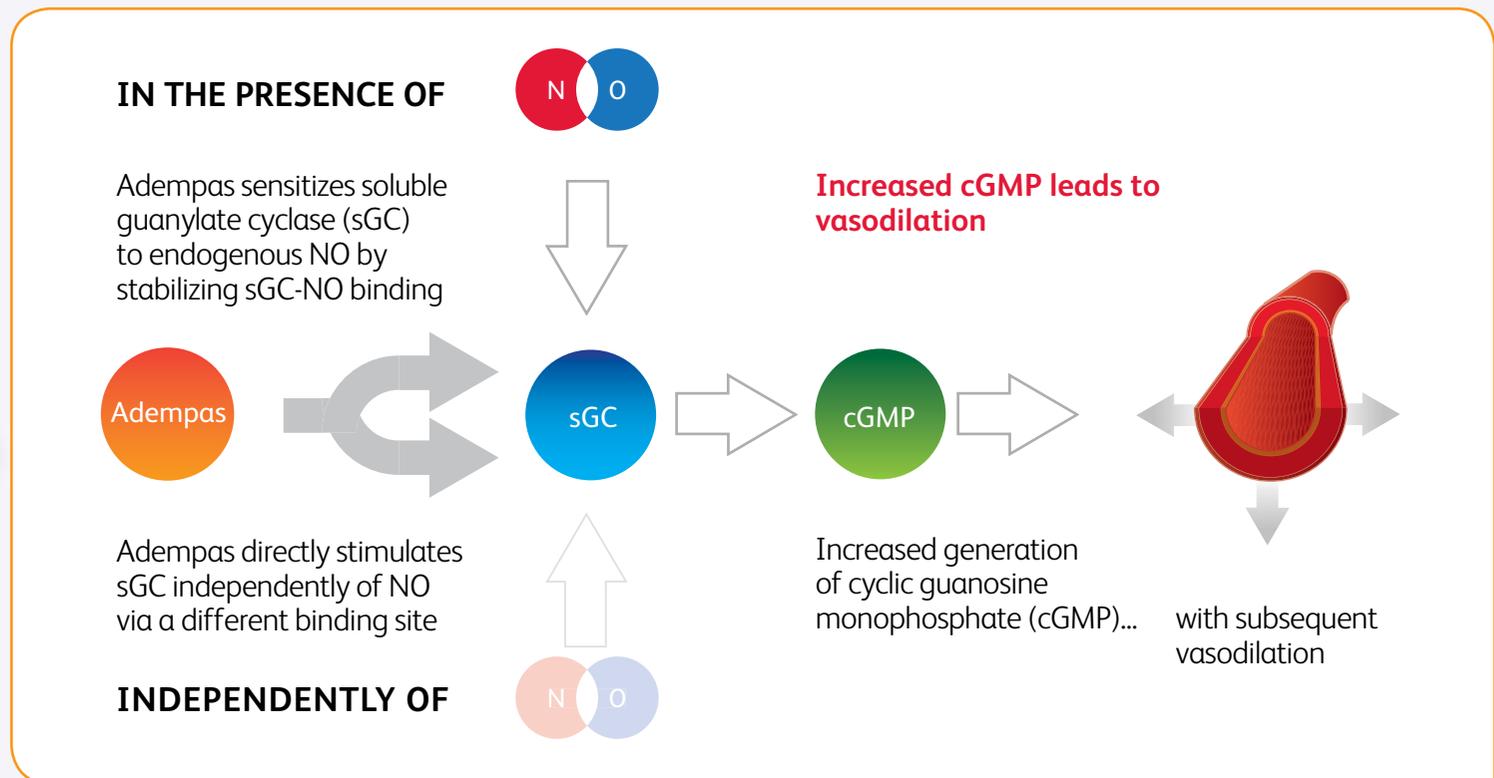
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## Adempas stimulates sGC regardless of NO levels to produce more cGMP

### Adempas has a dual mode of action



**36**  
METERS

**mean improvement in 6-minute walk distance (6MWD) over placebo at Week 12 for adults with PAH (WHO Group 1) (95% Confidence Interval [CI]: 20m-52m; p<0.001)**

**PATENT-1:** A randomized, double-blind, placebo-controlled, Phase 3 study.

443 PAH patients were studied. (Adempas 2.5 mg n=254, 1.5 mg n=63, placebo n=126)

Baseline characteristics:

- PAH defined as: pulmonary vascular resistance (PVR) >300 dyn·sec·cm<sup>-5</sup>, mean pulmonary arterial pressure (mPAP) >25 mm Hg
- Mean age: 51 years (approximately 80% female)
- PAH etiologies: idiopathic (61%), familial (2%), associated with connective tissue disease (25%), congenital heart disease (8%), portal hypertension (3%), or anorexigen or amphetamine use (1%)
- Mean 6MWD was 363m
- Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

Patient population was: 50% treatment-naïve, 44% pretreated with an endothelin receptor antagonist (ERA), and 6% pretreated with a prostacyclin analogue (PCA). The majority of patients had WHO functional class II (42%) or III (54%) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

### CONTRAINDICATIONS

Adempas is contraindicated in:

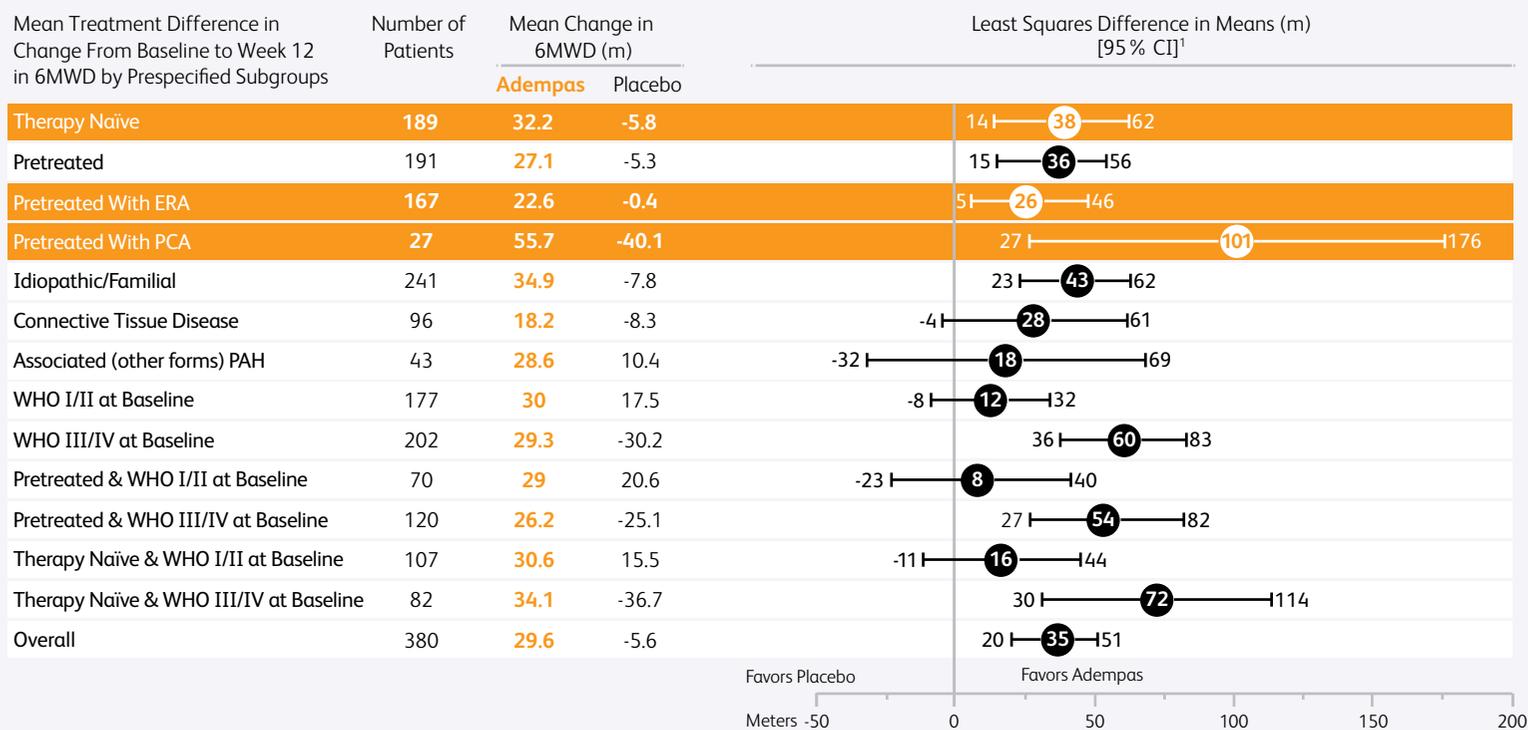
- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).



# Adempas demonstrates efficacy in treatment naïve patients, as monotherapy or in combination with ERA or PCA in PAH (WHO Group 1)

With Adempas, PAH (WHO Group 1) patients can remain on current therapies\* and still see additional efficacy

## \*Studied in combination with ERAs and PCAs



FOR PAH

## WARNINGS AND PRECAUTIONS

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

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

Important requirements of the Adempas REMS program include the following:

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

Further information, including a list of certified pharmacies, is available at [www.AdempasREMS.com](http://www.AdempasREMS.com) or 1-855-4ADEMPAS.



Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.

# BE IN THE **NO**

## WARNINGS AND PRECAUTIONS (continued)

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

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

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

## MOST COMMON ADVERSE REACTIONS

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

**For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.**

### Reference:

1. Clinical Study Report No. A62510. Data on file. Bayer.

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## ADEMPAS (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

### BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at [www.adempas-us.com](http://www.adempas-us.com).

#### WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)
- Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)
- For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).

## 1 INDICATIONS AND USAGE

### 1.1 Chronic-Thromboembolic Pulmonary Hypertension

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

### 1.2 Pulmonary Arterial Hypertension

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

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

## 4 CONTRAINDICATIONS

### 4.1 Pregnancy

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

### 4.2 Nitrates and Nitric Oxide Donors

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

### 4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.2)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Embryo-Fetal Toxicity

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

### 5.2 Adempas REMS Program

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

Important requirements of the Adempas REMS Program include the following:

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

Further information, including a list of certified pharmacies, is available at [www.AdempasREMS.com](http://www.AdempasREMS.com) or 1-855-4 ADEMPAS.

### 5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular

outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

### 5.4 Bleeding

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

### 5.5 Pulmonary Veno-Occlusive Disease

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

## 6 ADVERSE REACTIONS

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

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

### 6.1 Clinical Trials Experience

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

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

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

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

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

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

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

## 7 DRUG INTERACTIONS

### 7.1 Pharmacodynamic Interactions with Adempas

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

**PDE Inhibitors:** Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see *Contraindications* (4.3) and *Clinical Pharmacology* (12.2)]. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

## 7.2 Pharmacokinetic Interactions with Adempas

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category X

##### Risk Summary

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

##### Animal Data

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

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

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

### 8.6 Females and Males of Reproductive Potential

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with

Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see *Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)*].

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

### 8.7 Renal Impairment

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

### 8.8 Hepatic Impairment

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

## 10 OVERDOSAGE

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

## 17 PATIENT COUNSELING INFORMATION

### See FDA-approved patient labeling (Medication Guide).

#### Embryo-Fetal Toxicity

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

#### Adempas REMS Program

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

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

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

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

#### Other Risks Associated with Adempas

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

Manufactured for:



**Bayer HealthCare**

Bayer HealthCare Pharmaceuticals Inc.  
Whippany, NJ 07981

Manufactured in Germany

Issued May 2014

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6710501BS

## ADEMPAS (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

### BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at [www.adempas-us.com](http://www.adempas-us.com).

#### WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)
- Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)
- For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).

## 1 INDICATIONS AND USAGE

### 1.1 Chronic-Thromboembolic Pulmonary Hypertension

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

### 1.2 Pulmonary Arterial Hypertension

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

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

## 4 CONTRAINDICATIONS

### 4.1 Pregnancy

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

### 4.2 Nitrates and Nitric Oxide Donors

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

### 4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.2)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Embryo-Fetal Toxicity

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

### 5.2 Adempas REMS Program

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

Important requirements of the Adempas REMS Program include the following:

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

Further information, including a list of certified pharmacies, is available at [www.AdempasREMS.com](http://www.AdempasREMS.com) or 1-855-4 ADEMPAS.

### 5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular

outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

### 5.4 Bleeding

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

### 5.5 Pulmonary Veno-Occlusive Disease

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

## 6 ADVERSE REACTIONS

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

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

### 6.1 Clinical Trials Experience

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

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

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

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

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

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

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

## 7 DRUG INTERACTIONS

### 7.1 Pharmacodynamic Interactions with Adempas

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

**PDE Inhibitors:** Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see *Contraindications* (4.3) and *Clinical Pharmacology* (12.2)]. Clinical experience with co-administration of Adempas and

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

## 7.2 Pharmacokinetic Interactions with Adempas

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category X

##### Risk Summary

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

##### Animal Data

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

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

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

### 8.6 Females and Males of Reproductive Potential

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with

Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see *Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)*].

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

### 8.7 Renal Impairment

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

### 8.8 Hepatic Impairment

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

## 10 OVERDOSAGE

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

## 17 PATIENT COUNSELING INFORMATION

### See FDA-approved patient labeling (Medication Guide).

#### Embryo-Fetal Toxicity

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

#### Adempas REMS Program

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

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

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

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

#### Other Risks Associated with Adempas

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

Manufactured for:



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Bayer HealthCare Pharmaceuticals Inc.  
Whippany, NJ 07981

Manufactured in Germany

Issued May 2014

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6710501BS

## INDICATIONS

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

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

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

## ADEMPAS CLINICAL STUDY DESIGNS

**PATENT-1:** A randomized, double-blind, placebo-controlled, Phase 3 study.

443 PAH patients were studied. (Adempas 2.5 mg n=254, 1.5 mg n=63, placebo n=126)

Baseline characteristics:

- PAH defined as: pulmonary vascular resistance (PVR) >300 dyn·sec·cm<sup>-5</sup>, mean pulmonary arterial pressure (mPAP) >25 mm Hg
- Mean age: 51 years (approximately 80 % female)
- PAH etiologies: idiopathic (61 %), familial (2 %), associated with connective tissue disease (25 %), congenital heart disease (8 %), portal hypertension (3 %), or anorexigen or amphetamine use (1 %)
- Mean 6MWD was 363m
- Concomitant medications: Oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed

Patient population was: 50 % treatment-naïve, 44 % pretreated with an endothelin receptor antagonist (ERA), and 6 % pretreated with a prostacyclin analogue (PCA). The majority of patients had WHO functional class II (42 %) or III (54 %) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

**CHEST-1:** A randomized, double-blind, placebo-controlled, Phase 3 study.

261 CTEPH patients were studied. (Adempas n=173, placebo n=88)

Baseline characteristics:

- Mean age: 59 years (range: 18–80)
- Mean 6MWD was 347m
- Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed, but not nitric oxide donors, endothelin receptor antagonists, prostacyclin analogues, specific phosphodiesterase (PDE)-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline)

Patient population was: 72 % inoperable by pulmonary endarterectomy (PEA) (pulmonary vascular resistance [PVR] >300 dyn·sec·cm<sup>-5</sup> and mean pulmonary arterial pressure >25 mm Hg measured at least 90 days after the start of full anticoagulation); 28 % recurrent or persisting pulmonary hypertension (PH) following PEA (PVR >300 dyn·sec·cm<sup>-5</sup> measured at least 180 days following PEA). The majority of patients were WHO functional class II (31 %) or III (64 %) at baseline. Patients with systolic blood pressure <95 mm Hg were excluded.

## IMPORTANT SAFETY INFORMATION

### WARNING: EMBRYO-FETAL TOXICITY

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

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

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

## CONTRAINDICATIONS

Adempas is contraindicated in:

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.
- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

**Please see additional Important Safety Information, including Boxed Warning, on following pages, and Brief Summary of the Prescribing Information on the previous pages.**

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FOR PAH. FOR CTEPH.  
**Adempas**<sup>®</sup>  
riociguat tablets  
0.5mg | 1mg | 1.5mg | 2mg | 2.5mg  
Adempas-US.com



## Adempas improves exercise capacity and delays time to clinical worsening\* in PAH

Patients walked farther with Adempas at Week 12: results from Week 2 onward

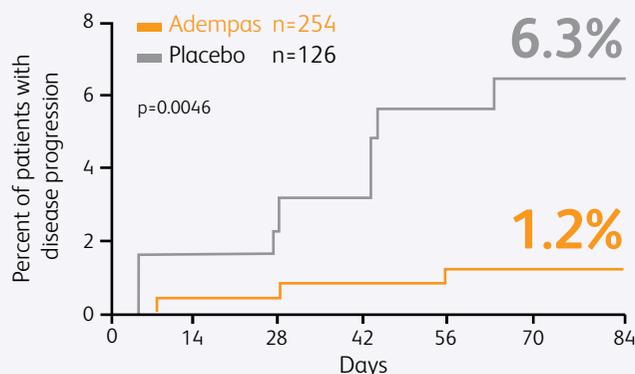
**36**  
METERS

mean improvement in 6-minute walk distance (6MWD) over placebo at Week 12 for adults with PAH (WHO Group 1) (95% Confidence Interval [CI]: 20m-52m;  $p < 0.001$ )

Adempas significantly delays the time to clinical worsening\*

Adempas improved pulmonary vascular resistance (PVR) at Week 12<sup>†</sup>

### Time to Clinical Worsening in the 12-Week Trial



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

**PVR**  
Secondary endpoint

$p < 0.001$

**-226 dyn·sec·cm<sup>-5</sup>**  
(95% CI:  
-281 to -170)

Right heart catheterization was performed at the beginning and end of the study period in 339 patients.  
<sup>†</sup>Placebo-adjusted mean change from baseline.

## WARNINGS AND PRECAUTIONS

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

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

Important requirements of the Adempas REMS program include the following:

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

Further information, including a list of certified pharmacies, is available at [www.AdempasREMS.com](http://www.AdempasREMS.com) or 1-855-4ADEMPAS.

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

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



# Adempas improves exercise capacity and WHO functional class in CTEPH\*

\*Inoperable or persistent/recurrent after surgery

## Patients walked farther with Adempas at Week 16: results from Week 2 onward

**46**  
METERS

mean improvement in 6-minute walk distance (6MWD) over placebo at Week 16 for adults with CTEPH (WHO Group 4) (95% Confidence Interval [CI]: 25m-67m;  $p < 0.001$ )

### Adempas improves WHO functional class

**2x**

as many CTEPH patients improved WHO functional class vs placebo ( $p = 0.0026$ ); Adempas:  $n = 57/173$  [33%], placebo:  $n = 13/87$  [15%] at Week 16.

#### Deteriorated

5% for Adempas  
( $n = 9/173$ )

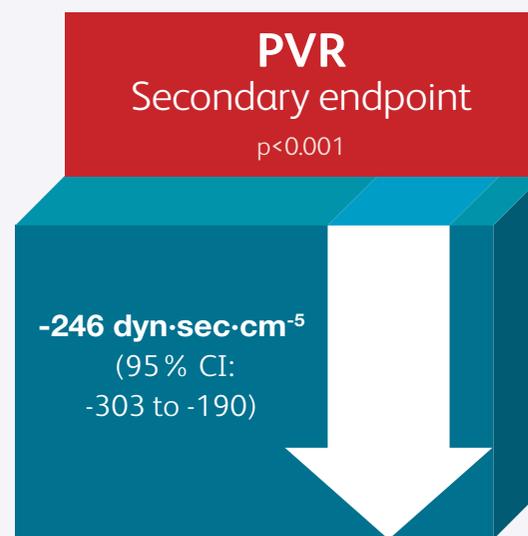
7% for placebo  
( $n = 6/87$ )

#### Stable

62% for Adempas  
( $n = 107/173$ )

78% for placebo  
( $n = 68/87$ )

### Adempas improved pulmonary vascular resistance (PVR) at Week 16<sup>†</sup>



Right heart catheterization was performed at the beginning and end of the study period in 233 patients.  
<sup>†</sup>Placebo-adjusted mean change from baseline.

## WARNINGS AND PRECAUTIONS (continued)

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

## MOST COMMON ADVERSE REACTIONS

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

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information on previous pages.

FOR PAH. FOR CTEPH.

**Adempas<sup>®</sup>**  
riociguat tablets

0.5mg | 1mg | 1.5mg | 2mg | 2.5mg

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# BE IN THE

PAH (WHO Group 1) and CTEPH (WHO Group 4) are associated with impaired synthesis of nitric oxide (NO)



## kNOw why to check YES for Adempas

### Some considerations include

NO YES

- Stimulates soluble guanylate cyclase (sGC) regardless of NO levels to produce more cyclic guanosine monophosphate (cGMP)
- Efficacy was shown in adults with PAH (WHO Group 1) in predominantly WHO functional class II-III\*
  - ✓ In combination with endothelin receptor antagonists (ERAs)
  - ✓ In combination with prostacyclin analogues (PCAs)
  - ✓ On Adempas monotherapy
- Improves exercise capacity and WHO functional class in persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH adult patients
- Improves exercise capacity, WHO functional class, and delays time to clinical worsening in PAH (WHO Group 1) adult patients<sup>†</sup>
- Offers comprehensive at-home nursing services, through the Aim Patient Support Program

**Adempas—the first and only treatment approved for PAH and CTEPH adult patients**

### INDICATIONS

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

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

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

**Please see additional Important Safety Information, including Boxed Warning, inside ad and Brief Summary of Prescribing Information inside.**

### IMPORTANT SAFETY INFORMATION

#### WARNING: EMBRYO-FETAL TOXICITY

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

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

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



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