VOL. 14 • NO. 6 • JUNE 2019

CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

# Undiagnosed OSA can double cardiovascular risk after surgery

Courtesy Dr. Matthew T.V. Chan

Dr. Matthew T.V. Chan and colleagues stated, "General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia."

**BY BIANCA NOGRADY**
*MDedge News*

Unrecognized severe obstructive sleep apnea is a risk factor for cardiovascular complications after major noncardiac surgery, according to a study published in JAMA.

The findings indicate that perioperative mismanagement of obstructive sleep apnea can lead to serious medical consequences. "General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia. Each of these events exacerbates [obstructive sleep apnea] and may predispose patients to postoperative cardiovascular complications," said researchers who conducted the The Postoperative vascular complications in unrecognised Obstructive Sleep apnoea (POSA) study (NCT01494181).

They undertook a prospective observational cohort study involving 1,218 patients undergoing major noncardiac surgery, who were already considered at high risk of postoperative cardiovascular events – having, for example, a history of coronary artery disease, stroke, diabetes, or renal impairment. However, none had a prior diagnosis of obstructive sleep apnea.

Preoperative sleep monitoring revealed that two-thirds of the cohort had unrecognized and

**OSA** // *continued on page 6*

# Smoking rates remain steady among the poor

**BY ANDREW D. BOWSER**
*MDedge News*

While an increasing number of U.S. citizens are saying no to cigarettes, current smoking rates are holding steady among people who face multiple forms of socioeconomic or health-related disadvantages, a recent study shows.

The odds of current smoking, versus never smoking, declined significantly during 2008-2017 for individuals with none of six disadvantages tied to cigarette use, including disability, unemployment, poverty, low education, psychological distress, and heavy alcohol intake, according to researchers.

Individuals with one or two of those disadvantages have also been cutting back, the data suggest. But, by contrast, odds of current versus never smoking did not significantly change for those with three or more disadvantages, according to Adam M. Leventhal, PhD, of the University of Southern California, Los Angeles, and coinvestigators.

"How this pattern can inform a cohesive policy agenda is unknown, but it is clear from these findings that the crux of the recently expanding tobacco-related health disparity problem in the

**Smoking** // *continued on page 7*

**INSIDE HIGHLIGHT**

CHEST® INSPIRATION: Pacing the Future

**NEWS FROM CHEST**

**Envisioning the future: The CHEST Environmental Scan**

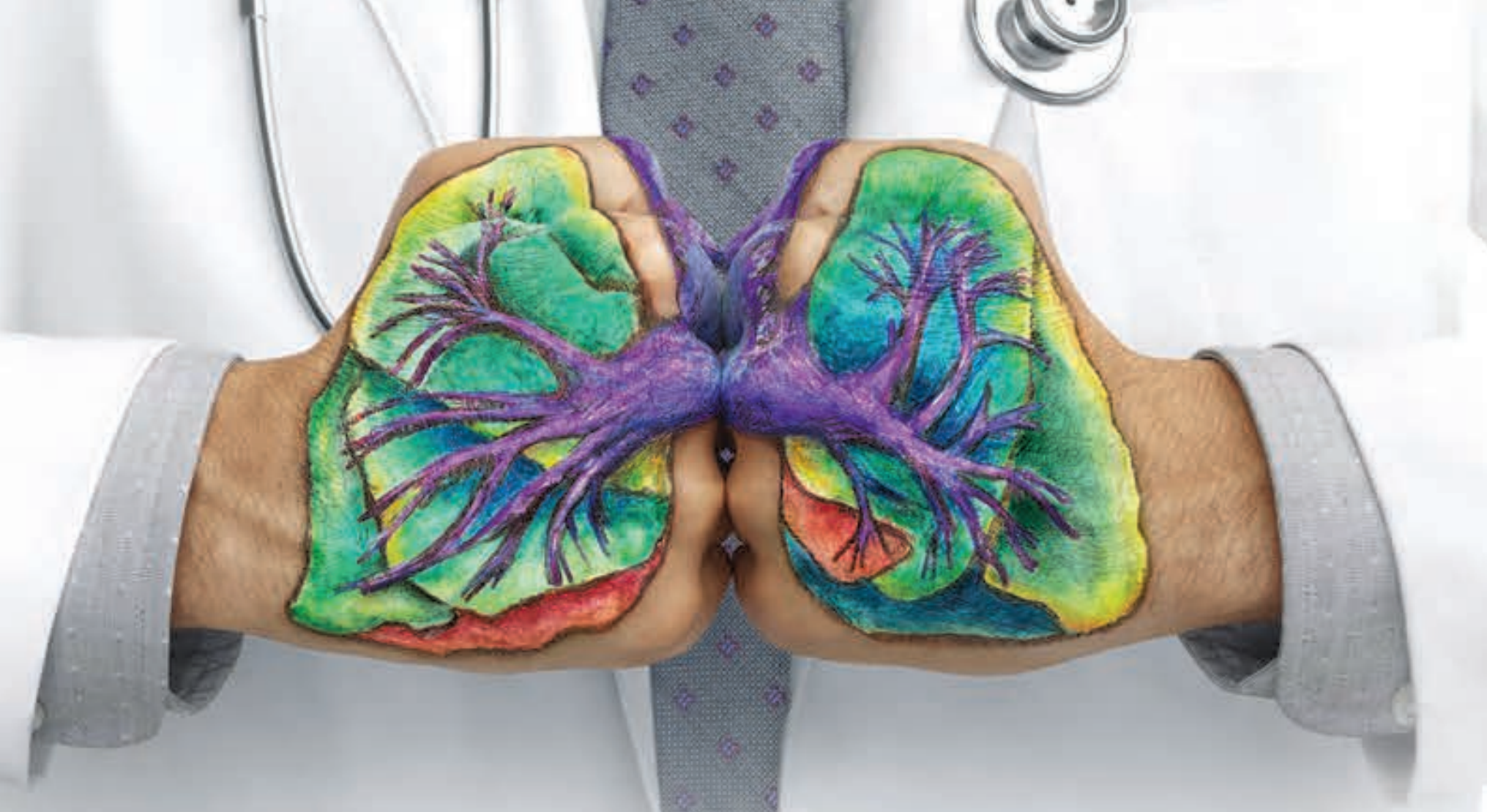
*Page 44*



CHEST Physician
10255 W Higgins Road,
Suite 280
Rosemont, IL 60018

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY



## Indication

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

## Select Important Safety Information

**Elevated liver enzymes:** Patients treated with Esbriet had a higher incidence of ALT and/or AST elevations of ≥3× ULN (3.7%) compared with placebo patients (0.8%). In some cases, these have been associated with concomitant elevations in bilirubin. No Esbriet-related cases of liver transplant or death due to liver failure have been reported. However, combined elevations of transaminases and bilirubin without evidence of obstruction is considered an important predictor of severe liver injury that could lead to death or the need for a transplant.

Measure ALT, AST, and bilirubin levels prior to initiating Esbriet, then monthly for the first 6 months, and every 3 months thereafter. Dosage modifications or interruption may be necessary.

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

**Gastrointestinal (GI) disorders:** Patients treated with Esbriet had a higher incidence of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease (GERD), and abdominal pain. GI events required dose reduction or interruption in 18.5% of 2403 mg/day Esbriet-treated patients, compared with 5.8% of placebo patients; 2.2% of 2403 mg/day Esbriet-treated patients discontinued treatment due to a GI event, compared with 1.0% of placebo patients. The most common (>2%) GI events leading to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary.

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

**Drug Interactions:**

CYP1A2 inhibitors: Concomitant use of Esbriet and strong CYP1A2 inhibitors (e.g., fluvoxamine) is not recommended, as CYP1A2 inhibitors increase systemic exposure of Esbriet. If discontinuation of the CYP1A2 inhibitor prior to starting Esbriet is not possible, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet.

Concomitant use of ciprofloxacin (a moderate CYP1A2 inhibitor) at the dosage of 750 mg BID and Esbriet are not recommended. If this dose of ciprofloxacin cannot be avoided, dosage reductions of Esbriet are recommended, and patients should be monitored.

Moderate or strong inhibitors of both CYP1A2 and other CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

CYP1A2 inducers: Concomitant use of Esbriet and strong CYP1A2 inducers should be avoided, as CYP1A2 inducers may decrease the exposure and efficacy of Esbriet.

**Specific Populations:**

Mild to moderate hepatic impairment: Esbriet should be used with caution in patients with Child Pugh Class A and B. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

Severe hepatic impairment: Esbriet is not recommended for patients with Child Pugh Class C. Esbriet has not been studied in this patient population.

Genentech

*A Member of the Roche Group*

# WE WON'T BACK DOWN FROM IPF

## Help preserve more lung function. Reduce lung function decline.[1–3]

### STUDIED IN A RANGE OF PATIENTS

Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[4]

### DEMONSTRATED EFFICACY

In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF[1–4]*

### ESTABLISHED SAFETY AND TOLERABILITY


The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[1†]

### COMMITTED TO PATIENTS

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

### WORLDWIDE PATIENT EXPERIENCE

More than 37,000 patients have taken pirfenidone worldwide[4§]

**Mild ($CL_{cr}$ 50-80 mL/min), moderate ($CL_{cr}$ 30-50 mL/min), or severe ($CL_{cr}$ <30 mL/min) renal impairment:** Esbriet should be used with caution. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed.

**End-stage renal disease requiring dialysis:** Esbriet is not recommended. Esbriet has not been studied in this patient population.

**Smokers:** Smoking causes decreased exposure to Esbriet which may affect efficacy. Instruct patients to stop smoking prior to treatment and to avoid smoking when using Esbriet.

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

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

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

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

IPF=idiopathic pulmonary fibrosis.

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

†In clinical trials, serious adverse reactions, including elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders, have been reported with Esbriet. Some adverse reactions with Esbriet occurred early and/or decreased over time (ie, photosensitivity reactions and gastrointestinal events).[1]

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

§The safety of pirfenidone has been evaluated in more than 1400 subjects, with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.[1]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

# Employed physicians now outnumber independents

BY ALICIA GALLEGOS
*MDedge News*

For the first time, employed physicians outnumber independent physicians, according to a survey from the American Medical Association.

The AMA's annual Physician Practice Benchmark Survey, which queried 3,500 doctors, showed that 47% of all physicians in 2018 were employed, compared with 46% of doctors who were self-employed that year. The number of employed physicians has risen 6 percentage points since 2012, while the number of self-employed doctors has fallen by 7 percentage points over the same period, according to the study published May 6 on the AMA website.

Younger physicians and women doctors were more likely to be employed than their counterparts. Nearly

70% of physicians under age 40 years were employees in 2018, compared with 38% of physicians 55 years and older, the study found. About 35% of physicians worked either directly for a hospital or in a practice at least partly owned by a hospital in 2018, up from 29% in 2012.

More than half of physicians surveyed (54%) worked in physician-owned practices in 2018 either as an owner, employee, or contractor, a decrease from 60% in 2012. Male physicians were more likely to be practice owners than female physicians. Among female doctors, 58% were employees, compared with 34% who were practice owners, while 52% of men physicians were practice owners, compared with 42% who were employees.

Surgical subspecialists had the highest share of owners (65%) followed by obstetrician-gynecologists (54%) and internal medicine subspecialists (52%). Emergency physicians had the lowest share of owners (26%) and the highest share of independent contractors (27%). Family physicians, meanwhile, had the highest share of employed physicians (57%).

A majority of doctors still work in small practices, the analysis found. In 2018, 57% of physicians worked in practices with 10 or fewer physicians versus 61% in 2012. However, fewer physicians work in solo practice. Between 2012 and 2018 the percentage of physicians in solo practice fell from 18% in 2012 to 15% in 2018.

The AMA's Physician Practice Benchmark Survey is a nationally representative survey of post-residency physicians who provide at least 20 hours of patient care per week, are not employed by the federal government, and practice in one of the 50 states or the District of Columbia. The 2018 survey was conducted in September 2018, and the final data included 3,500 physicians.

agallegos@mdedge.com

## VIEW ON THE NEWS

**Michael E. Nelson, MD, FCCP, comments:** Today one hears of physician early retirement and burnout, and now data that reveal that most doctors are choosing employment over ownership. With the hyperbolic expansion of administrative tasks related to government oversight, the institution of the electronic records, the ever-increasing cost of overhead, among many other pressures, it is not difficult to understand why physicians choose not to "own" a practice. If one transfers those headaches to someone else, the practice of medicine should be simplified. But as an employee, physicians are often judged more by their Press-Ganey score than how well they practice medicine. There is also a crowd of corporate clerks whose job it is to count things and tell you why you are not doing your job correctly or efficiently, while knowing nothing of what your job entails. In addition, most employment contracts contain a "termination without cause" clause that allows the employer to fire you without giving you a reason. I believe owning a practice may be less frightening.

## Sedation amplies OSA risk // *continued from page 1*

untreated obstructive sleep apnea, including 11.2% with severe obstructive sleep apnea.

At 30 days after surgery, patients with obstructive sleep apnea had a 49% higher risk of the primary outcome of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, or stroke, compared with those without obstructive sleep apnea.

However, this association was largely due to a significant 2.23-fold higher risk among patients with severe obstructive sleep apnea, while those with only moderate or mild sleep apnea did not show a significant increased risk of cardiovascular complications.

Patients in this study with severe obstructive sleep apnea had a 13-fold higher risk of cardiac death, 80% higher risk of myocardial injury, more than 6-fold higher risk of heart failure, and nearly 4-fold higher risk of atrial fibrillation.

Researchers also saw an association between obstructive sleep apnea and increased risk of infective outcomes, unplanned tracheal intubation, postoperative lung ventilation, and readmission to the ICU.

The majority of patients received nocturnal oximetry monitoring during their first 3 nights after surgery. This revealed that patients without obstructive sleep apnea had significant increases in oxygen desaturation index during their first night after surgery, while those with sleep apnea did not return to their baseline oxygen desaturation index until the third night after surgery.

"Despite a substantial decrease in ODI [oxygen desaturation index] with oxygen therapy in patients with OSA during the first 3 postoperative nights, supplemental oxygen did not modify the association between OSA and postoperative cardiovascular event," wrote Matthew T.V. Chan, MD, of Chinese University of Hong Kong, Prince of Wales Hospital, and coauthors.

Given that the events were associated with longer durations of severe oxyhemoglobin desaturation, more aggressive interventions such as positive airway pressure or oral appliances may be required, they noted.

"However, high-level evidence demonstrating the effect of these measures on perioperative outcomes is lacking [and] further clinical trials are now required to test if additional monitoring or alternative interventions would reduce the risk," they wrote.

The study was supported by the Health and Medical Research Fund (Hong Kong), National Healthcare Group–Khoo Teck Puat Hospital, University Health Network Foundation, University of Malaya, Malaysian Society of Anaesthesiologists, Auckland Medical Research Foundation, and ResMed. One author declared grants from private industry and a patent pending on an obstructive sleep apnea risk questionnaire used in the study.

chestphysiciannews@chestnet.org

**SOURCE:** Chan MTV et al. JAMA. 2019;321(18):1788-98. doi: 10.1001/jama.2019.4783.

### VIEW ON THE NEWS

**Wake-up call on OSA surgery risk**

This study is large, prospective, and rigorous, and adds important new information to the puzzle of the impact of sleep apnea on postoperative risk, Dennis Auckley, MD, FCCP, and Stavros Memtsoudis, MD, wrote in an editorial accompanying this study. The study focused on predetermined clinically significant and measurable events, used standardized and objective sleep apnea testing, and attempted to control for many of the confounders that might have influenced outcomes.

The results suggest that obstructive sleep apnea should be recognized as a major perioperative risk factor, and it should receive the same attention and optimization efforts as comorbidities such as diabetes.

*Dr. Auckley is from the division of pulmonary, critical care and sleep medicine at MetroHealth Medical Center, Case Western Reserve University, Cleveland, and Dr. Memtsoudis is clinical professor of anesthesiology at Cornell University, New York. These comments are adapted from an editorial (JAMA. 2019;231[18]:1775-6). Both declared board and executive positions with the Society of Anesthesia and Sleep Medicine. Dr. Auckley declared research funding from Medtronic, and Dr. Memtsoudis declared personal fees from Teikoku and Sandoz.*



***CHEST PHYSICIAN* IS ONLINE**

*CHEST Physician is available at chestphysician.org.*

David A. Schulman, MD, FCCP, is Medical Editor in Chief of *CHEST Physician*.

CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



**CHEST PHYSICIAN**, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to CHEST members. Content for **CHEST PHYSICIAN** is provided by Frontline Medical Communications Inc. Content for News From Chest is provided by the American College of Chest Physicians.



**POSTMASTER:** Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Services, 10255 W Higgins Road, Suite 280, Rosemont, IL 60018-9914.

**RECIPIENT:** To change your address, contact Subscription Services at 1-800-430-5450. For paid subscriptions, single issue purchases, and missing issue claims, call Customer Service at 1-833-836-2705 or e-mail custsvc.chph@fulcoinc.com

**CHEST PHYSICIAN** (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434, fax 973-206-9378.

**EDITORIAL OFFICES** 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

**ADVERTISING OFFICES** 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378



FRONTLINE MEDICAL COMMUNICATIONS

**Frontline Medical Communications Society Partners**

**VP/GROUP PUBLISHER; DIRECTOR, FMC SOCIETY PARTNERS** Mark Branca
**EDITOR IN CHIEF** Mary Jo M. Dales
**EXECUTIVE EDITORS** Denise Fulton, Kathy Scarbeck
**EDITOR** Therese Borden
**CREATIVE DIRECTOR** Louise A. Koenig
**DIRECTOR, PRODUCTION/MANUFACTURING** Rebecca Slebodnik
**DIRECTOR, BUSINESS DEVELOPMENT** Monique Michowski, 973-206-8015, cell 732-278-4549, mmichowski@mdedge.com
**DIGITAL ACCOUNT MANAGER** Rey Valdivia 973-206-8094 rvaldivia@mdedge.com
**CLASSIFIED SALES REPRESENTATIVE** Drew Endy 215-657-2319, cell 267-481-0133 dendy@mdedge.com
**SENIOR DIRECTOR OF CLASSIFIED SALES** Tim LaPella, 484-921-5001, tlapella@mdedge.com

**FRONTLINE MEDICAL COMMUNICATIONS**
**Corporate**
**PRESIDENT/CEO** Alan J. Imhoff
**CFO** Douglas E. Grose
**SVP, FINANCE** Steven J. Resnick
**VP, OPERATIONS** Jim Chicca
**VP, SALES** Mike Guire
**VP, SOCIETY PARTNERS** Mark Branca
**VP, EDITOR IN CHIEF** Mary Jo M. Dales
**VP, EDITORIAL DIRECTOR, CLINICAL CONTENT** Karen Clemments
**CHIEF DIGITAL OFFICER** Lee Schweizer
**VP, DIGITAL CONTENT & STRATEGY** Amy Pfeiffer
**PRESIDENT, CUSTOM SOLUTIONS** JoAnn Wahl
**VP, CUSTOM SOLUTIONS** Wendy Raupers
**VP, MARKETING & CUSTOMER ADVOCACY** Jim McDonough
**VP, HUMAN RESOURCES & FACILITY OPERATIONS** Carolyn Caccavelli
**DATA MANAGEMENT DIRECTOR** Mike Fritz
**CIRCULATION DIRECTOR** Jared Sonners
**CORPORATE DIRECTOR, RESEARCH & COMMS.** Lori Raskin
**DIRECTOR, CUSTOM PROGRAMS** Patrick Finnegan

**In affiliation with Global Academy for Medical Education, LLC**
**PRESIDENT** David J. Small, MBA

# New guidance on TB screens for health care workers

**BY BIANCA NOGRADY**
*MDedge News*

U.S. health care personnel no longer need to undergo routine tuberculosis testing in the absence of known exposure, according to new screening guidelines from the National Tuberculosis Controllers Association and Centers for Disease Control and Prevention.

The revised guidelines on tuberculosis screening, testing, and treatment of U.S. health care personnel, published in Morbidity and Mortality Weekly Report, are the first update since 2005. The new recommendations reflect a reduction in concern about U.S. health care personnel's risk of occupational exposure to latent and active tuberculosis infection.

Lynn E. Sosa, MD, from the Connecticut Department of Public Health and National Tuberculosis Controllers Association, and coauthors wrote that rates of tuberculosis infection in the United States have declined by 73% since 1991, from 10.4/100,000 population in 1991 to 2.8/100,000 in 2017. This has been matched by similar declines among health care workers, which the authors said raised questions about the cost-effectiveness of the previously recommended routine serial occupational testing.

"In addition, a recent retrospective cohort study of approximately 40,000 health care personnel at a tertiary U.S. medical center in a low TB-incidence state found an extremely low rate of TST conversion (0.3%) during 1998-2014, with a limited proportion attributable to occupational exposure," they wrote.

The new guidelines recommend health care personnel undergo baseline or preplacement tuberculosis testing with an interferon-gamma release assay (IGRA) or a tuberculin skin test (TST), as well as individual risk assessment and symptom evaluation.

The individual risk assessment considers whether the person has lived in a country with a high tuberculosis rate, whether they are immunosuppressed, or whether they have had close contact with someone with infectious tuberculosis.

This risk assessment can help decide how to interpret an initial positive test result, the authors said.

"For example, health care personnel with a positive test who are asymptomatic, unlikely to be infected with *M. [Mycobacterium] tuberculosis*, and at low risk for progression on the basis of their risk assessment should have a second test (either an IGRA or a TST) as recommended in the 2017 TB diagnostic guidelines of the American Thoracic Society, Infectious Diseases Society of America, and CDC," they wrote. "In this example, the health care personnel should be considered infected with *M. tuberculosis* only if both the first and second tests are positive."

*"In addition, a recent retrospective cohort study of approximately 40,000 health care personnel at a tertiary U.S. medical center in a low TB-incidence state found an extremely low rate of TST conversion (0.3%) during 1998-2014, with a limited proportion attributable to occupational exposure."*

After that baseline testing, personnel do not need to undergo routine serial testing except in the case of known exposure or ongoing transmission. The guideline authors suggested serial screening might be considered for health care workers whose work puts them at greater risk – for example, pulmonologists or respiratory therapists – or for those working in settings in which transmission has happened in the past.

For personnel with latent tuberculosis infection, the guidelines recommend "encouragement of treatment" unless it is contraindicated, and annual symptom screening in those not undergoing treatment.

The guideline committee also advocated for annual tuberculosis education for all health care workers.

The new recommendations were based on a systematic review of 36 studies of tuberculosis screening and testing among health care personnel, 16 of which were performed in the United States.

The authors stressed that recommendations from the 2005 CDC guidelines – which do not pertain to health care personnel screening, testing, treatment and education – remain unchanged.

One author declared personal fees from the National Tuberculosis Controllers Association during the conduct of the study. Two others reported unrelated grants and personal fees from private industry. No other conflicts of interest were disclosed.

chestphysiciannews@chestnet.org

**SOURCE:** Sosa LE et al. MMWR. 2019;68:439-43.

## Economic disadvantages have cumulative impact on smoking risk

// *continued from page 1*

United States is not tied to groups facing merely a single form of disadvantage," Dr. Leventhal and coauthors wrote in a report on the study in JAMA Internal Medicine.

The cross-sectional analysis by Dr. Leventhal and colleagues was based on National Health Interview Survey (NHIS) data from 2008 to 2017 including more than 278,000 respondents aged 25 years or older.

A snapshot of that 10-year period showed that current smoking prevalence was successively higher depending on the number of socioeconomic or health-related disadvantages.

The mean prevalence of current smoking over that entire time period was just 13.8% for people with zero of the six disadvantages, 21.4% for those with one disadvantage, and so on, up to 58.2% for those with all six disadvantages, according to data in the published report.

Encouragingly, overall smoking prevalence fell from 20.8% in 2008-2009 to 15.8% in 2016-2017, the researchers found. However, the decreasing trend was not apparent for individuals with many disadvantages.

The odds ratio for change of smoking per year was 0.951 (95% confidence interval, 0.944-0.958) for those with zero disadvantages, 0.96 (95% CI, 0.95-0.97) for one disadvantage, and 0.98 (95% CI, 0.97-0.99) for two, all representing significant annual reductions in current versus never smoking, investigators said. By contrast, no such significant changes were apparent for those with three, four, five, or six such disadvantages.

Tobacco control or regulatory policies that consider these disadvantages separately may be overlooking a "broader pattern" showing that the cumulative number of disadvantages correlates with the magnitude of disparity, wrote Dr. Leventhal and colleagues in their report.

"Successful prevention of smoking initiation and promotion of smoking cessation in multi-disadvantaged populations would substantially reduce the smoking-related public health burden in the United States," they concluded.

Dr. Leventhal and colleagues reported no conflicts related to their research, which was supported in part by a Tobacco Centers of Regulatory Science award from the National Cancer Institute and the Food and Drug Administration, among other sources.

chestphysiciannews@chestnet.org

**SOURCE:** Leventhal AM. et al. JAMA Intern Med. 2019 Apr 22. doi: 10.1001/jamainternmed.2019.0192.

TERROA/ISTOCK/GETTY IMAGES

# Eosinophils key to glucocorticoid response in asthma

**BY WILL PASS**
*MDedge News*

Patients with mild asthma who rely solely on short-acting beta2-agonists (SABAs) to control their asthma symptoms remain at increased risk of exacerbations, according to investigators.

Two recent studies presented at the American Thoracic Society's international conference demonstrated the benefits of glucocorticoid therapy among patients with mild persistent or intermittent asthma while highlighting differential responses to steroids among patients with high versus low levels of eosinophils in sputum. Both studies were simultaneously published in the New England Journal of Medicine.

The first study, SIENA, led by Stephen C. Lazarus, MD of the University of California, San Francisco, and colleagues, involved 295 patients with mild, persistent asthma. Patients were classified as having either a high or low level of eosinophils in sputum, with a low level defined by two sputum samples consisting of less than 2% eosinophils. After a single-blind placebo run-in period of 6 weeks, patients were randomized to receive either mometasone (an inhaled glucocorticoid), tiotropium (a long-acting muscarinic antagonist [LAMA]), or placebo for 12 weeks each, with subsequent crossover through the two remaining treatments. The primary outcome was the response to each active agent, compared with placebo among low-eosinophil patients who had a differential response to a trial agent.

Out of 295 patients, 221 (75%) had low eosinophils and 74 (25%) had high eosinophils. In the low-eosinophil subgroup, 59% of patients had a differential response to a trial agent; among these, 57% responded better to mometasone, compared with 43% who responded better to placebo, and 60% responded better to tiotropium, compared with 40% who responded better to placebo.

Turning to secondary analyses, among patients with high eosinophil levels who had a differential response, 74% responded better to mometasone, compared with 26% who responded better to placebo, and 57% responded better to tiotropium, compared with 43% who responded better to placebo.

In an additional exploratory analysis, adults with low eosinophil levels had better responses to tiotropium than placebo (62% vs 38%).

The researchers stated that a key finding of the study is that three-quarters of the mild, persistent asthma population had low eosinophil levels, far fewer than expected and that the difference in their response to mometasone compared to tiotropium was not significant.

"Our results raise the question of whether treatment guidelines should be reevaluated for patients with mild, persistent asthma for whom evidence of type 2 inflammation is lacking," the investigators wrote. "The need for a change in treatment strategy is further highlighted by a growing body of literature suggesting that mild, persistent asthma can be managed safely without the daily use of inhaled glucocorticoids and by data showing that patients with a low eosinophil level may not have a favorable response to inhaled glucocorticoids" (New Engl J Med. 2019 May 19. doi: 10.1056/NEJMoa1814917).

The second study, Novel START, conducted by lead author Richard Beasley, DSc, of the Medical Research Institute of New Zealand, Wellington, and colleagues, compared the efficacy of two inhaled glucocorticoid regimens and albuterol alone for patients with mild persistent or intermittent asthma, measured by annualized exacerbation rate.

Initial randomization involved 675 patients, of whom 668 were included in the final analysis. Patients were randomized into three groups: albuterol as needed (100 mcg, two inhalations as needed for asthma symptoms), budesonide maintenance (200 mcg, one inhalation twice daily with as-needed albuterol), or budesonide/formoterol (budesonide 200 mcg and formoterol 6 mcg, one inhalation as needed). Along with annualized exacerbation rate, several secondary outcomes assessed symptoms, respiratory function, and number of severe exacerbations.

Data analysis showed that patients in the budesonide groups had similar rates of annualized exacerbation, both of which were significantly better than the exacerbation rate in the albuterol-only group; the absolute rate of exacerbations per patient per year was 0.175, 0.195, and 0.400 for budesonide maintenance, budesonide/formoterol, and albuterol only, respectively. Similarly, the median fraction of exhaled nitric oxide (FENO) was lower in the budesonide groups than in the albuterol-only group. Patients in the budesonide/formoterol group had a 56% lower relative risk of severe pulmonary exacerbation than patients in the budesonide maintenance group and a 60% lower relative risk than the albuterol group. However, maintenance budesonide provided better symptom relief than budesonide/formoterol, "which suggests that for the patient for whom asthma symptoms rather than exacerbations are the most bothersome, maintenance treatment has value," the investigators wrote (New Engl J Med. 2019 May 19. doi: 10.1056/NEJMoa1901963).

"The findings of our trial are consistent with evidence regarding the treatment of moderate and severe asthma – that maintenance and reliever therapy" with inhaled glucocorticoid/formoterol "results in a lower risk of severe exacerbations than maintenance therapy with an inhaled glucocorticoid–[long-acting beta agonist] and as-needed SABA," the investigators concluded.

SIENA was funded by National Heart, Lung, and Blood Institute, with medications provided by Boehringer Ingelheim, Merck, and Teva; the investigators reported relationships with Sanofi, Vectura, Circassia, DBV Technologies, and others. Novel START was funded by AstraZeneca and the Health Research Council of New Zealand; the investigators reported relationships with GlaxoSmithKline, Genentech, Theravance Biopharma, and others.

**chestphysiciannews@chestnet.org**

**SOURCES:** Beasley R et al. New Engl J Med. 2019 May 19. doi: 10.1056/NEJMoa1901963; Lazarus SC et al. New Engl J Med. 2019 May 19. doi: 10.1056/NEJMoa1814917.

## VIEW ON THE NEWS

**Daniel Ouellette, MD, FCCP, comments:** In my city clinic, I see many patients with difficult-to-treat asthma. They are often young, poor, underinsured, and obese. The obstacles are many: co-pays are too high; patients' health literacy is low; medications are too often ineffective; and oral corticosteroids are continued indefinitely by other providers. Novel biologic agents can be unrealistic as a result of denied coverage and patient concerns about injectable medicines. New advances may help. Checking sputum eosinophil levels as an outpatient and targeting therapy in these patients may lead to improved outcomes from cost-effective strategies. Intermittent, as needed, combination ICS/LABA may be an effective, sensible, and affordable alternative for many with mild disease.

StockPlanets/E+/Getty Images

# REVATIO OS
## gives you another option to help patients make strides.

Including tablet and injection, you have **3 dosage forms** for treating pulmonary hypertension (PAH).

Prescribe the form that best meets your patients' needs.


**The first PDE5 inhibitor in an OS (oral suspension) for PAH.**

Revatio®
sildenafil

## Indication

REVATIO is a phosphodiesterase-5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71%) or associated with connective tissue disease (25%).

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

## Important Safety Information

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

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

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

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

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

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

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

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

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

Limited published data from randomized controlled trials, case-controlled trials, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy. There are risks to the mother and fetus from untreated PAH.

Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation.

The most common side effects of REVATIO greater than or equal to 3% were epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. 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.

The Revatio® Family

Available in OS, tablet, and injection forms.

**Learn more at REVATIOHCP.com**

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

Revatio® sildenafil 20 mg tablets

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

## INDICATION AND USAGE

REVATIO is a phosphodiesterase (PDE-5) indicated for the treatment of pulmonary arterial hypertension (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 (CTD) (25%).

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

## DOSAGE AND ADMINISTRATION

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

**Reconstitution of the Powder for Oral Suspension** 1. Tap the bottle to release the powder. 2. Remove the cap. 3. Accurately measure out 60 mL of water and pour the water into the bottle. 4. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 5. Remove the cap. 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Remove the cap. 9. Press the bottle adaptor into the neck of the bottle. The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

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

## CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

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

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

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

**Epistaxis** The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist). The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

**Visual Loss** When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥ 50 per year in the general population. An observational case-crossover study evaluated risk of NAION when PDE-5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to the PDE-5 inhibitor in a prior time period. The results suggest an approximately 2-fold increase in the risk of NAION with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies. 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® (sildenafil)-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.

In a placebo-controlled fixed dose titration study (Study 2) of REVATIO (starting with recommended dose of 20 mg and increased to 40 mg and then 80 mg all three times a day) as an adjunct to intravenous epoprostenol in patients with PAH, the adverse reactions that were more frequent in the REVATIO + epoprostenol group than in the epoprostenol group (greater than 6% difference) are shown in Table 2.

**Table 2: Adverse Reactions (%) in patients with PAH in Study 2 (incidence in REVATIO + Epoprostenol group at least 6% greater than Epoprostenol group)**

| | REVATIO + Epoprostenol (n=134) | Epoprostenol (n=131) | (REVATIO + Epoprostenol) minus Epoprostenol |
|---|---|---|---|
| Headache | 57 | 34 | 23 |
| Edema^ | 25 | 13 | 14 |
| Dyspepsia | 16 | 2 | 14 |
| Pain in extremity | 17 | 6 | 11 |
| Diarrhea | 25 | 18 | 7 |
| Nausea | 25 | 18 | 7 |
| Nasal congestion | 9 | 2 | 7 |

^includes peripheral edema

**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.

# AFib on the rise in patients with COPD hospitalized for exacerbations

BY JEFF CRAVEN

**FROM THE JOURNAL *CHEST*®** ▪ Atrial fibrillation is being seen with increasing frequency in patients admitted to U.S. hospitals for exacerbations of end-stage chronic obstructive pulmonary disease, based on a retrospective analysis of data from the U.S. Nationwide Inpatient Sample.

The prevalence of atrial fibrillation (AFib) among patients with end-stage chronic obstructive pulmonary disease (COPD) on home oxygen who were admitted with COPD exacerbations increased from 12.9% in 2003 to 21.3% in 2014, according to Xiaochun Xiao of the department of health statistics at Second Military Medical University in Shanghai and colleagues.

Additionally, "we found that comorbid [AFib] was associated with an increased risk of the need for mechanical ventilation, especially invasive mechanical ventilation. Moreover, comorbid [AFib] was associated with adverse clinical outcomes, including increased in-hospital death, acute respiratory failure, acute kidney injury, sepsis, and stroke," the researchers wrote in the study published in the journal CHEST.

Patients included in the study were aged at least 18 years, were diagnosed with end-stage COPD and on home oxygen, and were hospitalized because of a COPD-related exacerbation. Based on 1,345,270 weighted hospital admissions of adults with end-stage COPD on home oxygen who met the inclusion criteria for the study, 18.2% (244,488 admissions) of patients had AFib, and the prevalence of AFib in COPD patients increased over time from 2003 (12.9%) to 2014 (21.3%; *P* less than .0001).

Patients with AFib, compared with patients without AFib, were older (75.5 years vs. 69.6 years; *P* less than .0001) and more likely to be male (50.7% vs. 59.1%; *P* less than .0001) and white (80.9% vs. 74.4%; *P* less than .0001). Patients with AFib also had higher stroke risk reflected in higher CHA2DS2-VASc scores (3.26 vs. 2.45; *P* less than .0001), and higher likelihood of in-hospital mortality and readmission reflected in Elixhauser scores greater than or equal to 4 (51.2% vs. 35.6%).

Larger hospitals in terms of number of beds, urban environment, and Medicare insurance status also were associated with a higher AFib prevalence.

AFib was associated with an increased cost of $1,415 and an increased length of stay of 0.6 days after adjustment for potential confounders. AFib also predicted risk for several adverse events, including stroke (odds ratio, 1.80; in-hospital death, [OR, 1.54]), invasive mechanical ventilation (OR, 1.37), sepsis (OR, 1.23), noninvasive mechanical ventilation (OR, 1.14), acute kidney injury (OR, 1.09), and acute respiratory failure (OR, 1.09).

The researchers suggested that the reason for this increased Afib incidence may be an aging population, advancing AFib diagnostic approaches, increased AFib awareness improving AFib detection, an increase in the prevalence of AFib during the study period ocurring as a result of reduced AFib-related mortality, and finally, increasing trends in risk factors may also be involved in the increased of AFib.

The researchers noted the database could have potentially overinflated AFib prevalence, as they could not differentiate index admissions and readmissions. The database also does not contain information about secondary diagnoses codes present on admission.

"Our findings should prompt further efforts to identify the reasons for increased [AFib] prevalence and provide better management strategies for end-stage COPD patients comorbid with [AFib]," the researchers concluded.

This study was funded by a grant from the Fourth Round of the Shanghai 3-Year Action Plan on Public Health Discipline and Talent Program. The authors reported no relevant conflict of interest.

chestphysiciannews@chestnet.org

**SOURCE:** Xiao X et al. CHEST. 2019 Jan 23. doi: 10.1016/j.chest.2018.12.021.

# No raised risk of cardiovascular events for patients with COPD receiving aclidinium bromide

**BY HEIDI SPLETE**

*MDedge News*

Aclidinium bromide reduced exacerbations in adults with chronic obstructive pulmonary disease with no increased risk of major adverse cardiovascular events, compared with placebo, in a randomized trial of more than 3,000 patients.

Aclidinium, a long-acting muscarinic antagonist (LAMA), has been shown to reduce COPD exacerbation in the short term, but long-term effectiveness has not been examined, wrote Robert A. Wise, MD, FCCP, of Johns Hopkins University, Baltimore, and colleagues.

ASCENT-COPD is a multicenter, double-blind, randomized, placebo-controlled, parallel-group noninferiority study conducted at 522 sites in the United States and Canada. A paper on recent data from ASCENT-COPD, published in JAMA, supports early findings reported last year at the American Thoracic Society meeting.

The researchers randomized adults with COPD to a 400-mg dose of aclidinium bromide twice daily, or placebo. The average age of the patients was 67 years; 59% were men. The median exposure time to aclidinium or placebo was 365 days during the first year of treatment,

**Dr. Robert A. Wise**

and the median exposure overall was 495 days for aclidinium patients and 478 days for placebo patients.

Of the 2,537 patients who completed the study, 69 (3.9%) in the aclidinium group and 76 (4.2%) in the placebo group experienced a major adverse cardiovascular event (MACE, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke).

In addition, annual rates of moderate to severe COPD exacerbations were significantly lower in the aclidinium patients compared with placebo patients (0.44 vs. 0.57, *P* less than .001).

In a secondary analysis with a definition of MACE expanded to include heart failure, arrhythmias, or cerebrovascular disease, results remained similar between the groups; events occurred in 168 aclidinium patients (9.4%) and 160 placebo patients (8.9%). The rate of COPD exacerbations requiring hospitalization was significantly lower in aclidinium patients, compared with placebo patients (0.07 vs. 0.10, *P* = .006).

Overall, the most common treatment-emergent adverse events were similar in the aclidinium and placebo groups, respectively: pneumonia (6.1% vs. 5.8%), urinary tract infections (5.2% vs. 5.0%), and upper respiratory tract infections (4.8% vs. 5.6%). The most common serious adverse events (in at least 1% of patients) were pneumonia, atrial fibrillation, heart failure, and coronary artery disease. Dry mouth and urinary retention were rare, and occurred in less than 1% of patients in each group.

"No patient subgroup demonstrated a difference in efficacy except when analyzed by baseline COPD severity, in which the treatment benefit was observed only in patients with $FEV_1$ [forced expiratory volume in 1 second] of 50% predicted or less," the researchers noted. "This may be explained by the lower exacerbation rate seen in the placebo group in patients with moderate airway obstruction vs. severe or very severe obstruction," they said.

*"Outcomes of this trial add data to the long-standing controversy over the safety of LAMAs in COPD" and support the need for additional research.*

"Outcomes of this trial add data to the long-standing controversy over the safety of LAMAs in COPD" and support the need for additional research, they said.

The study findings were limited by several factors including insufficient power to detect cause-specific mortality and the use of a LAMA with low risk of systemic effects, the researchers noted.

chestphysiciannews@chestnet.org

**SOURCE:** Wise RA et al. JAMA. 2019. 321:1693-701.

# Survey: Americans support regulation of vaping products

**BY RICHARD FRANKI**

*MDedge News*

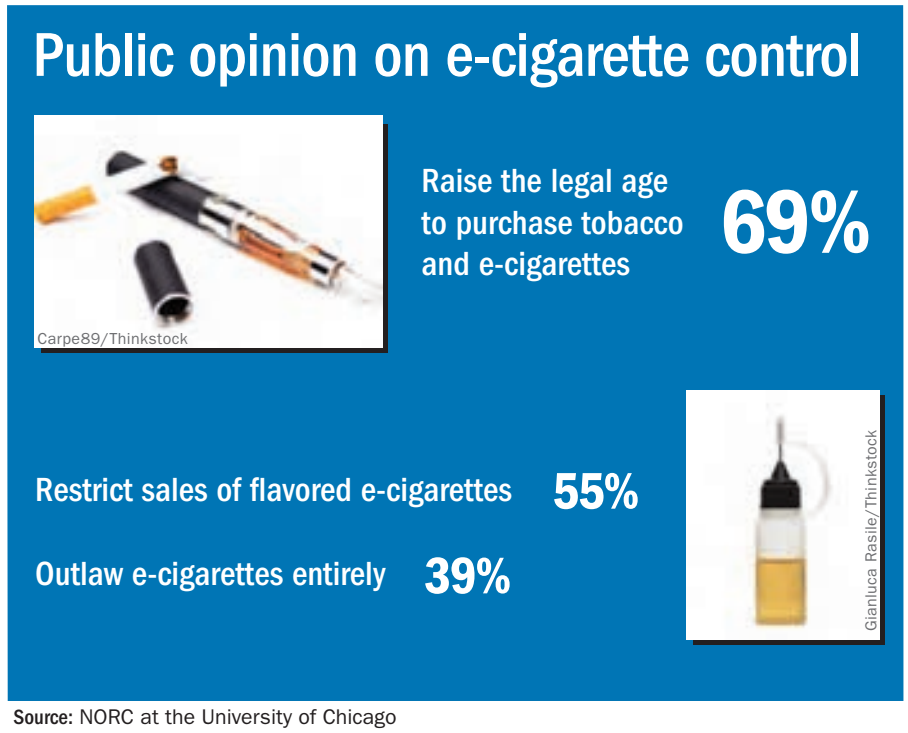
Almost 70% of adults believe that the Food and Drug Administration should raise the legal age to purchase e-cigarettes and tobacco, according to a new survey by NORC at the University of Chicago, a nonpartisan research institution.

"Americans are particularly concerned about teens becoming newly addicted to e-cigarettes, and they support a range of actions the federal government could take to make vaping products less available, less addictive, and less appealing," Caroline Pearson, senior vice president at NORC, said in a written statement.

The AmeriSpeak Spotlight on Health Poll, conducted Feb. 14-18, 2019 (margin of error, plus or minus 4.12%), showed that 69% of adults strongly or somewhat support raising the age limit to purchase e-cigarettes and tobacco and 55% support restricting sales of flavored e-cigarettes, NORC reported. Almost 40% of the 1,004 respondents expressed support for a complete ban on e-cigarettes.

Despite FDA efforts under Commissioner Scott Gottlieb, MD, to raise awareness of teen vaping, only 21% of those surveyed correctly responded that e-cigarettes generally contain more nicotine that regular cigarettes. Dr. Gottlieb announced his resignation recently, "but he indicated that the Trump Administration will continue efforts to increase regulation of e-cigarettes," NORC said.

rfranki@mdedge.com




**Source:** NORC at the University of Chicago

# In a tight vote, FDA panel backs mannitol for treatment of cystic fibrosis

**BY KARI OAKES**
*MDedge News*

A Food and Drug Administration Advisory Committee voted that the benefit-risk profile of an inhaled treatment for cystic fibrosis merits approval of the drug – dry powder mannitol (DPM).

Mannitol is a naturally occurring sugar alcohol that is used as a low-calorie sweetener; it is generally recognized as safe when taken enterically. Inhaled DPM, marketed as Aridol, is currently approved as a bronchoprovocation agent. For the current indication, DPM is given as 10x40-mg capsules twice daily.

In a 9-7 vote, the FDA's Pulmonary-Allergy Drugs Advisory Committee (PADAC) decided that DPM's modest potential to improve pulmonary function in adults with cystic fibrosis (CF) outweighed a potential signal for increased exacerbations seen in clinical trials.

Chiesi USA is seeking approval of DPM for the management of cystic fibrosis to improve pulmonary function in patients 18 years of age and older in conjunction with standard therapies. It plans to market DPM as Bronchitol.

Some committee members who voted against approval, including PADAC chair David H. Au, MD, worried that DPM's ease of use might prompt patients and caregivers to substitute it for inhaled hypertonic saline, a medication that's more burdensome to use but has a longer track record for efficacy and safety. While hypertonic saline requires cumbersome equipment and cleaning regimens and takes 20-30 minutes to administer, DPM is administered over about 5 minutes via a series of capsules inserted into a small inhaler device.

"I was very impressed by conversations that we heard from the community that this will be viewed as a substitute drug [for hypertonic saline]," said Dr. Au, professor of medicine at the University of Washington, Seattle. "Before we make that leap of faith ... we have to better understand how it has to be used." He also acknowledged that making the call for DPM was "challenging."

Other committee members were reassured by the fact that DPM is approved for adult use in 35 countries; it's been in use since 2011 in Australia for adults and children.

**Dr. John M. Kelso**

Some members also noted an unmet need in CF therapies and placed confidence in those treating CF patients to find ways to use DPM safely and effectively. "I'm really counting on the cystic fibrosis clinicians who do this for a living to figure out where to use this in their armamentarium," said John M. Kelso, MD, an allergist at Scripps Clinic, San Diego.

In 2012, the initial new drug application submitted by Pharmaxis, which then held marketing rights to DPM, resulted in a "no" vote for approval from PADAC, and eventual FDA denial of approval. The initial submission was supported by two phase 3 clinical trials, 301 and 302, that included pediatric patients. In the pediatric population, there was concern for increased hemoptysis with DPM, so the FDA advised the drug's marketers to consider seeking approval for an adult population only in its reapplication. The current submission followed a new double-blind, randomized, placebo-controlled trial, study 303, that included adults with CF aged 18 or over.

*The FDA panel decided that mannitol's modest potential to improve pulmonary function in adults with cystic fibrosis outweighed a potential signal for increased exacerbations seen in clinical trials.*

All three studies had similar designs, tracking change from baseline in forced expiratory volume in 1 second ($FEV_1$) from baseline to the end of the 26-week study period. In addition to this primary endpoint, secondary endpoints included other pulmonary function measures, as well as the number of protocol-defined pulmonary exacerbations (PDPEs). Participants also reported quality of life and symptom measures on the Cystic Fibrosis Questionnaire–Revised (CFQ-R).

In study 301, the dropout rate approached one in three participants with higher discontinuation in the intervention than the control arm, causing significant statistical problems in dealing with missing data. Thus, said the FDA's Robert Lim, MD, though this study had positive results for $FEV_1$, it was not "statistically robust."

The second study, 302, did not meet its primary endpoint, and there was "no support from secondary endpoints" for efficacy, said Dr. Lim, a clinical team leader in the FDA's Division of Pulmonary, Allergy, and Rheumatology Products.

The current submission was also supported by a new post hoc subgroup analysis of adults in studies 301 and 302. A total of 414 patients receiving DPM and 347 receiving placebo (DPM at a nontherapeutic level) were included in the integrated analysis of patients from all three studies. Studies 301 and 302 both had open-label extension arms, allowing more patients to be included in safety data.

The problems caused by the missing data from study 301 were addressed in the design of study 303 by encouraging patients who discontinued the study drug to continue data collection efforts for the study. Dropout rates were lower overall in study 303 and balanced between arms.

Over the 26-week duration of study 303, investigators saw a statistically significant improvement in $FEV_1$ of about 50 mL, according to the FDA's analysis. Post hoc analyses of studies 301 and 302 showed point estimate increases of approximately 80 mL, according to Dr. Lim.

In its presentations, Chiesi USA presented its integrated analysis of adult data from the three clinical trials. The analysis showed an increase in $FEV_1$ from baseline of 73 mL for the DPM group, compared with an increase of 7 mL for the control group, using an intention-to-treat population (*P* less than .001). The committee heard evidence that in adults with CF, pulmonary function typically decreases by 1%-3% annually.

The PDPE rate was slightly higher in the DPM group than in the control group in studies 302 and 303, but the differences were not statistically significant. These findings have a backdrop of an overall low rate of PDPEs ranging from 0.221 to 0.995 per year, according to Chiesi presenter Scott Donaldson, MD, a pulmonologist who directs the adult cystic fibrosis center at the University of North Carolina at Chapel Hill.

When looking at the subgroup of United States study participants, the DPM integrated cohort included more patients with a history of prior pulmonary exacerbations. In the DPM group, 45% of U.S. participants had at least one exacerbation in the prior year, and 20% had two or more exacerbations, compared with 38% and 14%, respectively, in the control group. Chiesi argued that this imbalance was likely responsible for the increased exacerbation rate.

*"This is not a drug for everybody; but absolutely, it's a drug for somebody. Ultimately we have to make that decision – I do think that we study populations, but we really take care of people."*

The sponsor and the FDA used different imputation methods to account for missing data from the earlier studies, complicating interpretation of the potential signal for increased exacerbations.

Quality of life data were similar between groups across the studies.

In the end, the view of the "yes" voters was encapsulated by James M. Tracy, DO, an allergist in private practice in Omaha, Neb. "This is not a drug for everybody; but absolutely, it's a drug for somebody. Ultimately we have to make that decision – I do think that we study populations, but we really take care of people."

The FDA usually follows the recommendations of its advisory panels.

koakes@mdedge.com


As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

# A PATH TO **ASTHMA CONTROL**

**DUPIXENT AFFECTS IL-4 AND IL-13 SIGNALING, IMPACTING TWO OF THE SOURCES THAT MEDIATE ALLERGIC AND EOSINOPHILIC INFLAMMATION[1]**

**The mechanism of dupilumab action in asthma has not been established.[1]**

## INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

### LIMITATION OF USE

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

## IMPORTANT SAFETY INFORMATION

**CONTRAINDICATION:** DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

### WARNINGS AND PRECAUTIONS

**Hypersensitivity:** Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

**Eosinophilic Conditions:** Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia, which may be associated with a reduction of oral corticosteroids. Cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

**Acute Asthma Symptoms or Deteriorating Disease:** Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

**LEARN MORE AT *DUPIXENTASTHMAHCP.COM***

**TRIAL 1:** BASELINE EOS ≥300 CELLS/µL

UP TO **81%**

## REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS through Week 24[1,a]

- **71% REDUCTION** with DUPIXENT 200 mg + SOC (n=65) vs placebo + SOC (n=68) (0.30 vs 1.04; rate ratio: 0.29 [95% CI: 0.11, 0.76])
- **81% REDUCTION** with DUPIXENT 300 mg + SOC (n=64) vs placebo + SOC (n=68) (0.20 vs 1.04; rate ratio: 0.19 [95% CI: 0.07, 0.56])

**TRIAL 1:** BASELINE EOS ≥300 CELLS/µL

UP TO **430 mL**

## IMPROVEMENT IN PRE-BRONCHODILATOR $FEV_1$ from baseline at Week 12[1]

- **430 mL IMPROVEMENT** with DUPIXENT 200 mg + SOC (n=65) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 260 mL [95% CI: 110, 400 mL])
- **390 mL IMPROVEMENT** with DUPIXENT 300 mg + SOC (n=64) vs **180 mL** with placebo + SOC (n=68) (LSM difference: 210 mL [95% CI: 60, 360 mL])

# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS (cont'd)

**Reduction of Corticosteroid Dosage:** Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation with DUPIXENT. 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) Infections:** It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

**TRIAL 1: 24-WEEK STUDY**–776 adults (≥18 years) with moderate-to-severe asthma on a standard of care of medium- or high-dose ICS and a LABA were randomized to either DUPIXENT 200 mg Q2W[b] + SOC (n=150), DUPIXENT 300 mg Q2W[c] + SOC (n=157), or placebo + SOC (n=158). Subjects enrolled in Trial 1 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. DUPIXENT was administered as an add-on to background asthma treatment. **Primary endpoint:** Mean change from baseline to Week 12 in $FEV_1$ in patients with baseline eosinophils ≥300 cells/µL. **Other endpoint:** Annualized rate of severe exacerbation events during the 24-week treatment period.[d] **Selected baseline demographics:** Mean duration of asthma: 22 years; mean exacerbations in previous year: 2.2; high-dose ICS use: 50%; pre-dose $FEV_1$ at baseline: 1.84 L; mean FeNO: 39 ppb; mean total IgE: 435 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[a] Severe exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
[b] With 400 mg loading dose.
[c] With 600 mg loading dose.
[d] Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LSM, least squares mean; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

**Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.**

DUPIXENT® (dupilumab) Injection
200mg • 300mg

# MORE PATIENTS STOPPED USING OCS WITH DUPIXENT WHILE IMPROVING ASTHMA CONTROL[1,2]

**TRIAL 3:** NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

**70%**

## REDUCTION IN OCS DOSE

(median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs **42%** (median 50%) with placebo + SOC (n=107)

**86% OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE** with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107)

## IMPROVE LUNG FUNCTION AND REDUCE SEVERE EXACERBATIONS WITH THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS, REGARDLESS OF PHENOTYPE[b]

**TRIAL 3:** NO BIOMARKER REQUIREMENT (ITT POPULATION)[a]

**59%**
**REDUCTION**

**IN ANNUALIZED RATE OF SEVERE EXACERBATIONS**
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63])

**220 mL**
**IMPROVEMENT**

**IN PRE-BRONCHODILATOR $FEV_1$**
at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL])

## IMPORTANT SAFETY INFORMATION

**ADVERSE REACTIONS:** The most common adverse reactions (incidence ≥1%) in asthma patients are injection site reactions, oropharyngeal pain, and eosinophilia.

**DRUG INTERACTIONS:** Avoid use of live vaccines in patients treated with DUPIXENT.

**TRIAL 3: 24-WEEK STUDY**–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107); the baseline mean OCS dose was 11 mg in the DUPIXENT group and 12 mg in the placebo group. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Selected baseline demographics:** Mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose $FEV_1$ at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

[a] Intention-to-treat (ITT) population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).
[b] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.
[c] With 600 mg loading dose.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

# DUPIXENT OFFERS A PATH TO ASTHMA CONTROL

| | DUPIXENT (dupilumab)[1] | XOLAIR® (omalizumab)[3] | NUCALA® (mepolizumab)[4] | FASENRA™ (benralizumab)[5] | CINQAIR® (reslizumab)[6] |
|---|---|---|---|---|---|
| Moderate asthma (eosinophilic phenotype) | ✓ | | | | |
| Severe asthma (eosinophilic phenotype) | ✓ | | ✓ | ✓ | ✓ |
| OCS-dependent asthma | ✓ | | | | |
| Pre-filled syringe | ✓ | ✓ | | ✓ | |
| At-home self-administration | ✓ | | | | |
| In-office administration | ✓ | ✓ | ✓ | ✓ | ✓ |

This presentation includes the fixed properties of these biologics. It is not intended to compare their safety, effectiveness, or uses. Please refer to each product's Prescribing Information for approved indication and dosing and administration information.

Xolair is indicated for moderate to severe persistent asthma in patients 6 years of age and older who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.[3]

## DUPIXENT IS THE FIRST ASTHMA BIOLOGIC TO OFFER THE CHOICE OF AT-HOME SELF-ADMINISTRATION OR IN-OFFICE ADMINISTRATION

**DUPIXENT can be administered in the office under the guidance of a healthcare provider if the patient is not an appropriate candidate for self-administration. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe.**

## IMPORTANT SAFETY INFORMATION

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

**Please see brief summary of full Prescribing Information on the following pages.**

**References: 1.** DUPIXENT Prescribing Information. March 2019. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485. **3.** Xolair Prescribing Information. September 2018. **4.** Nucala Prescribing Information. December 2017. **5.** Fasenra Prescribing Information. November 2017. **6.** Cinqair Prescribing Information. May 2016.

SANOFI GENZYME

REGENERON



US-DAS-1450

**DUPIXENT® (dupilumab) injection, for subcutaneous use** **Rx Only**
**Brief Summary of Prescribing Information**

## 1 INDICATIONS AND USAGE

### 1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

### 1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

## 4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

### 5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

### 5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

### 5.4 Acute Asthma Symptoms or Deteriorating Disease

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

### 5.5 Reduction of Corticosteroid Dosage

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

### 5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

### 5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

## 6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*

### 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.

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT plus TCS to placebo plus TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

**Table 1: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16**

| Adverse Reaction | DUPIXENT Monotherapy[a] | | DUPIXENT + TCS[b] | |
|---|---|---|---|---|
| | DUPIXENT 300 mg Q2W[c] N=529 n (%) | Placebo N=517 n (%) | DUPIXENT 300 mg Q2W[c] + TCS N=110 n (%) | Placebo + TCS N=315 n (%) |
| Injection site reactions | 51 (10) | 28 (5) | 11 (10) | 18 (6) |
| Conjunctivitis[d] | 51 (10) | 12 (2) | 10 (9) | 15 (5) |
| Blepharitis | 2 (<1) | 1 (<1) | 5 (5) | 2 (1) |
| Oral herpes | 20 (4) | 8 (2) | 3 (3) | 5 (2) |
| Keratitis[e] | 1 (<1) | 0 | 4 (4) | 0 |
| Eye pruritus | 3 (1) | 1 (<1) | 2 (2) | 2 (1) |
| Other herpes simplex virus infection[f] | 10 (2) | 6 (1) | 1 (1) | 1 (<1) |
| Dry eye | 1 (<1) | 0 | 2 (2) | 1 (<1) |

[a] Pooled analysis of Trials 1, 2, and 4.

[b] Analysis of Trial 3 where subjects were on background TCS therapy.

[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3)

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject). The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

**Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)**

| Adverse Reaction | AS Trials 1 and 2 | | |
|---|---|---|---|
| | DUPIXENT 200 mg Q2W N=779 n (%) | DUPIXENT 300 mg Q2W N=788 n (%) | Placebo N=792 n (%) |
| Injection site reactions[a] | 111 (14%) | 144 (18%) | 50 (6%) |
| Oropharyngeal pain | 13 (2%) | 19 (2%) | 7 (1%) |
| Eosinophilia[b] | 17 (2%) | 16 (2%) | 2 (<1%) |

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions

*Conjunctivitis*

During the 52-week treatment period of concomitant therapy trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Warnings and Precautions (5.2)]*.

*Eczema Herpeticum and Herpes Zoster*

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group

(1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

*Hypersensitivity Reactions*

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

*Eosinophils*

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

*Cardiovascular (CV)*

In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, non-fatal myocardial infarctions [MI], and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), CV thromboembolic events (CV deaths, non-fatal MIs, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

## 7 DRUG INTERACTIONS

### 7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

### 7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.

Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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 an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

### 8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

### 8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.2) in the full prescribing information]*. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in $FEV_1$ (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

### 8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

## 10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

## 17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT 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 DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in 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 *[see Warnings and Precautions (5.5)]*.

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License # 1760; Marketed by sanofi-aventis U.S. LLC, (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) /DUPIXENT is a registered trademark of Sanofi Biotechnology/ Issue Date: March 2019 US-DUP-1246

# Circulating tumor cells predict NSCLC survival, but clinical role uncertain

BY WILL PASS

Dr. Colin Lindsay

Dr. Juergen Wolf

Will Pass/MDedge News

GENEVA – Circulating tumor cell (CTC) count is an independent predictor of both progression-free and overall survival in patients with advanced non–small cell lung cancer (NSCLC), according to data from 550 patients.

This is the largest CTC study to date and the first to compare test results from multiple centers, reported lead author Colin Lindsay, MD, PhD, of the University of Manchester (England) and colleagues. Among the centers, investigators found minimal variability in results guiding progression-free survival and no significant differences in results predicting overall survival. These findings suggest that CTC testing could be reproducible and reliable on a large scale, Dr. Lindsay said during a presentation at the European Lung Cancer Conference; he added that this conclusion addresses a previous concern about the process.

"A slight problem with the process is still that it is semi-automated," Dr. Lindsay said at the meeting presented by the European Society for Medical Oncology. "The machine will harvest potential cells and stain potential cells, but the end step of the process is that a trained user in each laboratory will decide which cell is a CTC and which cell isn't a CTC, and it's that potential for user variability that was the basis of this study."

The retrospective study involved 550 patients with NSCLC whose samples were processed at seven centers in multiple European countries, including 209 patients whose data were previously unpublished. The investigators looked for associations between CTC count and survival using Cox regression analysis and evaluated if CTCs could add value to prognostic clinicopathologic models based on c-indices and likelihood ratio statistics. CTC count was assessed as a continuous variable and, based on previous studies, using two categorical thresholds: at least 2 cells per 7.5 mL and at least 5 cells per 7.5 mL. In addition, the investigators looked for associations between NSCLC molecular subtypes and CTC levels.

The results showed that both cutoff levels were predictive of survival, with the higher threshold carrying a poorer prognosis. For progression-free survival, CTC counts of at least 2 cells per 7.5 mL carried a hazard ratio of 1.72, whereas the 5-cell threshold had a hazard ratio of 2.21 (*P* less than .001 for both). Similarly, overall survival hazard ratios for the lower and higher thresholds were 2.18 and 2.75, respectively (*P* less than .001 for both). When baseline CTC count was added to the analysis, predictive accuracy increased further, dropping *P* values 10-fold, down to .0001. C-index models had a more modest impact. Although minor heterogeneity was detected among centers for prediction of progression-free survival, overall survival data were broadly reliable. Dr. Lindsay noted that intercenter differences seemed to diminish with greater testing experience. No relationships were detected between molecular subtypes and CTC profiles.

"It's always good to finish a talk with the white elephant in the room," Dr. Lindsay said in his concluding remarks. "Is there room for CTCs in non–small cell lung cancer? I believe they have the potential to complement ctDNA work by offering a cellular context, but [CTCs] aren't there yet for clinical roll-out."

Invited discussant Juergen Wolf, MD, of the University Hospital Cologne (Germany) provided a similar conclusion, suggesting that CTCs have a clear place in research, but their clinical value is debatable. He noted that ctDNA, the most similar diagnostic and prognostic tool under development, has a pragmatic edge because ctDNA samples are more amenable to shipping and handling. Dr. Wolf noted that ctDNA also has been shown to have value for treatment planning, specifically for the EGFR T790M resistance mutation. This latter point tied into a larger issue described by Dr. Wolf, who suggested that in the current treatment landscape for NSCLC, predictive testing needs to be actionable.

"We cannot draw a consequence of a prognostic biomarker," Dr. Wolf said. "In the era of personalized medicine, what we need is predictive markers, predictive of the outcome of specific therapies."

The investigators disclosed financial relationships with AstraZeneca, Novartis, Pfizer, and others.

chestphysician@chestnet.org

**SOURCE:** Lindsay C et al. ELCC 2019, Abstract 210.

# Alirocumab reduces both type 1 and 2 MIs

**BY BRUCE JANCIN**
*MDedge News*

NEW ORLEANS – Lowering LDL cholesterol with alirocumab to levels below what's achievable with intensive statin therapy appears to be an important strategy for prevention of type 1 MI – and perhaps even more impressively, type 2 MI – following acute coronary syndrome, Harvey D. White, MD, reported at the annual meeting of the American College of Cardiology.

What's so important about the 23% reduction in risk of type 2 MI achieved with alirocumab (Praluent) relative to placebo documented in a prespecified secondary analysis from the ODYSSEY Outcomes trial?

"For type 2 MI, this is the first data indicating that a lipid-lowering therapy can attenuate risk," according to Dr. White, a cardiologist at Auckland (N.Z.) City Hospital.

The ODYSSEY Outcomes trial compared the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab to placebo in 18,924 patients with a recent acute coronary syndrome and an LDL cholesterol level of at least 70 mg/dL despite intensive statin therapy. At 4 months, the PCSK9 inhibitor plus statin therapy reduced participants' mean LDL by 54%, from 93 to 48 mg/dL, while the LDL level actually drifted upward in the control group on placebo plus statin therapy. In the previously reported primary results of this landmark randomized clinical trial, alirocumab on top of background intensive statin therapy reduced the primary composite endpoint of death attributable to coronary heart disease, ischemic stroke, MI, or unstable angina requiring hospitalization by 15%, compared with controls (N Engl J Med. 2018 Nov 29;379[22]:2097-107).

During a median 2.8 years of prospective follow-up, there were 1,860 new MIs in study participants. A blinded clinical events committee evaluated the myocardial infarctions according to the Third Universal Definition and determined 66% were type 1 MIs, 21% were type 2, and 13% were type 4, with lesser numbers of types 3 and 5 MI.

*"For type 2 MI, this is the first data indicating that a lipid-lowering therapy can attenuate risk."*

Alirocumab reduced the risk of any MI by 15%, with a 6.8% incidence during follow-up, compared with 7.9% on placebo. The risk of type 1 MI, typically attributable to plaque rupture, was reduced by 13%, with an incidence of 4.9% with alirocumab and 5.6% with placebo.

*Continued on following page*

## VIEW ON THE NEWS

**Jason Lazar, MD, FCCP, comments:** This study represents yet another important milestone in the broader incorporation of PCSK9 inhibitors for cardiovascular risk reduction. While 2013 American Heart Association/American College of Cardiology guidelines focused on statin dose (high or intermediate intensity) rather than specific LDL targets, the 2018 revised guidelines re-emphasized LDL treatment goals as well as the adjunct use of non-statin agents to achieve treatment goals. Specifically, for patients with atherosclerotic cardiovascular disease and for those at very high risk, high-intensity statin therapy was recommended to be used to obtain a 50% reduction in LDL cholesterol. The updated guidelines recommended the addition of ezetimide and PCSK9 inhibitors to statin therapy in patients not reaching treatment goals. While PCSK9 inhibitors are generally accepted to effectively lower LDL cholesterol markedly, their use has been limited by high cost and sparseness of data on clinical event reduction. Accordingly, more affordable pricing and the demonstration of clinical event reduction such as the ODYSSEY Trial will likely lead to expanded use of these agents. In addition, lowering of risk for both types 1 and 2 myocardial infarction, which are felt to result from plaque rupture and demand ischemia, respectively, suggest that lipid lowering in general may portend salutary pleiotropic effects that have been previously linked to statin therapy alone.

# When to transition HF patients to alternative loop diuretic

**BY ANDREW D. BOWSER**
*MDedge News*

PHILADELPHIA – While many internists might think a switch to spironolactone would be warranted for a heart failure patient with inadequate response to oral furosemide (Lasix), transitioning to an alternative loop diuretic may be the preferable approach, a cardiologist said at the annual meeting of the American College of Physicians.

"Lasix is associated with very high variability in terms of absorption, so torsemide and bumetanide should be considered in patients who have a poor response," said Paul McKie, MD, MPH, a cardiologist and internist with Mayo Clinic, Rochester, Minn., in a session at the meeting.

When polled, only 22% of attendees at the session picked "transition to torsemide" as the best approach for restoring fluid balance with the lowest adverse potential in a 74-year-old woman with nonischemic cardiomyopathy on furosemide 80 mg twice daily who has been hospitalized for fluid overload three times in the year.

The majority of attendees (41%) said they would have added spironolactone. Dr. McKie disagreed with this approach. Instead, Dr. McKie said he would have transitioned this person to an alternative loop diuretic.

"I think spironolactone is a great medication in heart failure with reduced ejection fraction, but the doses we typically use are generally suboptimal to achieve diuresis," he added.

The rationale for considering an alternative loop diuretic in this patient hinges on bioavailability, which is "highly variable" for oral furosemide, at 10%-100%, while by contrast, torsemide and bumetanide have a very consistent bioavailability of 80%-100%, according to Dr. McKie.

Andrew D. Bowser/MDedge News

**Dr. Paul McKie**

"For this reason, I think about using torsemide or bumetanide in patients who are not responding to oral Lasix," he said.

Dr. McKie described an algorithm that he and his colleagues use in clinic to intensify outpatient therapy for patients not achieving diuresis.

The first step is to ensure adherence and ask patients whether they are following sodium and fluid restriction: "I always ask about that first," he said. "I tell patients, 'You can out-eat and out-drink any diuretic regimen.' "

The next step is to double the dose of the loop diuretic and, sometimes, triple the dose if the double dose is not effective.

"If they're diuresing but it's just not adequate, then I'll move to twice-daily dosing," he said. "A practical tip is I tell patients to take their first dose as soon as they wake up and the second dose around 1:00 p.m. so that they're not urinating all night."

If twice-daily dosing doesn't help, then that's the point where an alternative loop diuretic would be warranted, according to Dr. McKie's algorithm.

"Then I add a thiazide like metolazone, but I only do that after I've increased the dose of the loop diuretic," he added.

If all else fails, then outpatient IV diuretics can be considered, according to the algorithmic approach.

Dr. McKie reported no relevant disclosures.

chestphysiciannews@chestnet.org

*Continued from previous page*

The risk reduction conferred by the PCSK9 inhibitor was even more robust for type 2 MI, the type caused by an oxygen supply/demand imbalance most commonly attributable to coronary artery spasm, coronary embolism, arrhythmias, anemia, hypertension, or hypotension: a 23% relative risk reduction as reflected in a 1.3% incidence in the alirocumab group, compared with a 1.7% rate in controls.

In contrast, alirocumab had no impact on the incidence of type 4 MI, a category that includes peri–

Bruce Jancin/MDedge News

**Dr. Harvey D. White**

*The beneficial effect of alirocumab on MI risk mostly involved a reduction in larger MIs – those with a biomarker peak greater than three times the upper limit of normal.*

percutaneous coronary intervention MIs as well as those attributable to stent thrombosis or restenosis.

The beneficial effect of alirocumab on MI risk mostly involved a reduction in larger MIs – those with a biomarker peak greater than three times the upper limit of normal.

An emphatic difference was found in the risk of death following type 1 as opposed to type 2 MI. Patients who experienced a type 1 MI during the study had an 11.9% mortality rate during an average of 1.6 years of post-MI follow-up, as compared with a 25.4% rate during 1.3 years of follow-up after a type 2 MI.

Alirocumab significantly reduced the risk of mortality following a type 1 MI, with a 10.2% rate as compared to 13.4% with placebo; that's a 31% relative risk reduction. Yet the PCSK9 inhibitor had no impact on the risk of death after a type 2 MI: 24.8% in the alirocumab group and 25.9% in controls.

Asked for his thoughts as to possible explanatory mechanistic pathways for the benefit of alirocumab in preventing type 2 MI, Dr. White noted that, in a Scottish study of the PCSK9 inhibitor evolocumab (Repatha), over the course of 72 months the drug appeared to reduce atherosclerotic progression and induce plaque stabilization and perhaps even regression.

"I think that's the probable mechanism. And we also know that statins improve endothelial function," he said.

He reported receiving research grant support and consultant fees from Sanofi and Regeneron, funders of the ODYSSEY Outcomes trial.

bjancin@mdedge.com

# High coronary artery calcium score points to CV risk

BY JIM KLING

Asymptomatic patients with coronary artery calcium (CAC) scores of 1,000 or higher should be considered at higher risk for cardiovascular disease and all-cause mortality than those with CAC scores of 400-999, based on data from a large retrospective study presented by Allison W. Peng at the annual meeting of the American College of Cardiology.

"Our data argues for consideration of CAC 1000 (or more) as a distinct group with CVD mortality greater than that of contemporary secondary prevention trials. ... We showed that those with CAC 1000 (or more) have both a higher area and density of calcification, a more dispersed pattern of calcification in their coronary artery tree (the majority with 4-vessel disease), with a

*Continued on following page*

*Continued from previous page*

markedly more diffuse distribution of extra-coronary calcification compared to the other CAC groups," Ms. Peng and her colleagues wrote in the study, which was published online in the Journal of the American College of Cardiology.

Future guidelines should address these patients as a distinct risk group that might gain the most benefit from targeted, aggressive preventive therapy, the researchers said.

Current guidelines identify individuals with CAC scores over 400 as the highest risk group. With a mean follow-up time of 12.3 years, the results from 66,636 asymptomatic individuals in the CAC consortium study, which included over 2,800 patients with CAC (Agatston) scores of 1,000 or more, indicate patients with CAC scores of 1000 or more have nearly a two-fold higher risk of CVD mortality compared to those with CAC scores of 400-999. While the mortality risk levels off slightly in those with scores exceeding 1,000, all-cause and cause-specific mortality risk still increases with no apparent upper CAC threshold.

Patients with a CAC score of at least 1,000 were 66.3 years old, on average; 86.3% were male, 52.4% had 4-vessel CAC, and they had a larger total CAC area.

Compared with patients with CAC scores of 400-999, those with a CAC score of 1,000 or more had a greater risk of cardiovascular dis-

ease (hazard ratio, 1.71; 95% confidence interval, 1.41-2.08), coronary heart disease (HR, 1.84; 95% CI, 1.43-2.36), cancer (HR, 1.36; 95% CI, 1.07-1.73), and all-cause mortality (HR, 1.51; 95% CI, 1.33-1.70).

Those with CAC scores of 400-999 had a 2.1, 3.6, 2.7, and 9.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively. But those with CAC scores of 1,000 of more had a 5.1, 8.0, 4.6, and 18.8 mortality rate per 1,000 person-years for CHD, CVD, cancer, and all-cause mortality, respectively.

The leading cause of death was CVD; 36.5% in the CAC 400-999 group and 42.6% in the CAC 1,000 or more group. CHD mortality, as a subset of CVD mortality, constituted 21.1% of deaths in the CAC 400-999 group and 27.1% of deaths in the CAC 1,000 or more group.

"Future randomized controlled trials of aggressive preventative therapies, for example PCSK9-inhibitors and anti-inflammatory drugs, in patients with CAC ≥ 1,000, may prove helpful to evaluate the benefits of such treatment in this unique group," the authors wrote. They also urged updating current guidelines.

The study was funded by the National Institutes of Health. The authors have no relevant financial disclosures.

**SOURCE:** Peng AW et al. JACC 2019. doi: 10.1016/S0735-1097(19)31894-7.

# PCV13 vaccine reduces frequency of otitis media visits

**BY HEIDI SPLETE**
*MDedge News*

The mean number of office visits for otitis media in children younger than 5 years dropped significantly after the introduction of the 13-valent pneumococcal conjugate vaccine, according to findings published in the International Journal of Pediatric Otorhinolaryngology.

Previous studies have shown that more than half of children with otitis media (OM) have serotypes included in the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), wrote Xiaofeng Zhou, MD, of Pfizer, New York, and colleagues.

To assess the impact of PCV13, with the additional serotypes 1, 3, 5, 6A, 7F, and 19A, the researchers analyzed data from the U.S. National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for three time periods: pre-PCV7 (1997-1999), after the introduction of PCV7 (2001-2009), and after the introduction of PCV13 (2011-2013).

Between the pre-PCV7 and PCV13 time periods, the researchers found significant reductions in the mean rates of OM visits of 48% and 41% among children younger than 2 years and younger than 5 years, respectively; reductions were 24% and 22%, respectively, when comparing PCV13 and PCV7.

For the PCV7 and PCV13 time periods, the mean number of OM visits per 100 children declined from 84 to 64 per 100 children younger than 2 years, from 41 to 34 per 100 children between ages 2 and 5 years, and from 59 to 46 per 100 children younger than 5 years.

The study findings were limited by several factors including the use of an ecologic study design, which was chosen to help reduce selection bias, but that did not show evidence of the field effectiveness of the PCV13 vaccine. Another limitation was the potential misclassification of patients with OM given clinician variability in diagnostic criteria, the researchers noted.

The investigators are employed by Pfizer, which funded the study.

chestphysiciannews@chestnet.org

**SOURCE:** Zhou X et al. Int J Pediatr Otorhinolaryngol. 2019 Apr. 119:96-102.

## VIEW ON THE NEWS

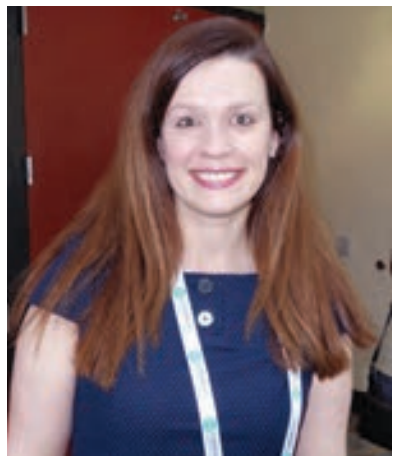
**Susan Millard, MD, FCCP, comments:** In the present era of vaccination skepticism by non-medical parent groups, Dr. Zhou's study is welcome news. Acute otitis media and recurrent otitis media cause missed days from school for children and work for parents, potential hearing issues, and frequent antibiotic use that has risk of emergence of resistant bacterial strains. Parents, pediatricians, and pediatric subspecialists will be excited to get this information.

# Combo respiratory pathogen tests miss pertussis

**BY M. ALEXANDER OTTO**
*MDedge News*

BALTIMORE – Comprehensive respiratory pathogen panels (RPAN) cannot be relied on to detect pertussis, according to an investigation from the University of Michigan, Ann Arbor.

Respiratory pathogen panels are popular because they test for many things at once, but providers have to know their limits, said lead investigator Colleen Mayhew, MD, a pediatric emergency medicine fellow at the University of Michigan.


Dr. Colleen Mayhew

"Should [the Respiratory Viruses Pathogen Panel] be used to diagnosis pertussis? No," she said at the Pediatric Academic Societies annual meeting. RPAN was negative for confirmed pertussis 44% of the time in the study.

"In our cohort, [it] was no better than a coin flip for detecting pertussis," she said. Also, even when it missed pertussis, it still detected other pathogens, which raises the risk that symptoms might be attributed to a different infection. "This has serious public health implications."

"The bottom line is, if you are concerned about pertussis, it's important to use a dedicated pertussis PCR [polymerase chain reaction] assay, and to use comprehensive respiratory pathogen testing only if there are other, specific targets that will change your clinical management," such as mycoplasma or the flu, Dr. Mayhew said.

In the study, 102 nasopharyngeal swabs positive for pertussis on standalone PCR testing – the university uses an assay from Focus Diagnostics – were thawed and tested with RPAN.

RPAN was negative for pertussis on 45 swabs (44%). "These are the potential missed pertussis cases if RPAN is used alone," Dr. Mayhew said. RPAN detected other pathogens, such as coronavirus, about half the time, whether or not it tested positive for pertussis. "Those additional pathogens might represent coinfection, but might also represent asymptomatic carriage." It's impossible to differentiate between the two, she noted.

In short, "neither positive testing for other respiratory pathogens, nor negative testing for pertussis by RPAN, is reliable for excluding the diagnosis of pertussis. Dedicated pertussis PCR testing should be used for diagnosis," she and her team concluded.

RPAN also is a PCR test, but with a different, perhaps less robust, genetic target.

The 102 positive swabs were from patients aged 1 month to 73 years, so "it's important for all of us to keep pertussis on our differential diagnose" no matter how old patients are, Dr. Mayhew said.

Freezing and thawing the swabs shouldn't have degraded the genetic material, but it might have; that was one of the limits of the study.

The team hopes to run a quality improvement project to encourage the use of standalone pertussis PCR in Ann Arbor. It might save money, because the tests cost the university around $400 each, instead of $700 for RPAN.

There was no industry funding. Dr. Mayhew didn't report any disclosures.

aotto@mdedge.com

### VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** Swabbing the nose to screen for infectious etiologies of respiratory infections such as pertussis, mycoplasma, respiratory syncytial virus, etc. is expensive but can be extremely helpful for specific populations at risk, such as immunocompromised patients, for example. I appreciate the information that using a panel to confirm pertussis may be inaccurate. Microbiology lab directors may block certain "extra tests" so we need more research on this topic to review sensitivity and specificity for different age groups tested.

# Role of mucin further delineated in CF pathogenesis

**BY CALEB RANS**
*MDedge News*

Mucin in children with cystic fibrosis precedes airway changes and infections, according to a cross-sectional cohort study.

It has been difficult for researchers to pinpoint the mechanisms that initiate lung disease in people with CF, because it is challenging to study young people with the disease and "CF animal models often fail to recapitulate aspects of human CF disease and yield disparate findings," wrote Charles R. Esther Jr., MD, of the division of pediatric pulmonology at the University of North Carolina at Chapel Hill and his colleagues in Science Translational Medicine.

They studied 46 clinically stable young children (aged 3.3 years, plus or minus 1.7 years) with CF and 16 age-matched controls who did not have CF, but had respiratory symptoms (aged 3.2 years, plus or minus 2.0 years) using chest CT imaging and bronchoalveolar lavage fluid. BALF samples in CF patients were collected over 62 study visits and subsequently cultured for detection and quantification of pathogens. The children with CF were enrolled in the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) program.

"We analyzed the relationships between airway mucus, inflammation, and bacterial culture/microbiome," the researchers wrote. BALF total mucin levels were higher in CF samples versus non-CF controls. In addition, Dr. Esther and his colleagues found that these results were the same regardless of infection status and that increased densities of mucus flakes were also seen in samples from the CF patients.

*"Elevated total mucin concentrations and inflammatory markers were observed in children with CF despite a low incidence of pathogens identified by culture or molecular microbiology."*

"Elevated total mucin concentrations and inflammatory markers were observed in children with CF despite a low incidence of pathogens identified by culture or molecular microbiology. This muco-inflammatory state also characterized our CF population with the earliest lung disease in the setting of little or no pathogen infection," they wrote.

Based on the findings, the investigators postulated that the airways of children with CF may show distinct defects in the clearance of recently created mucins, which could contribute to early CF lung disease.

A key limitation of the study was the prophylactic use of intermittent antibiotics. As a result, bacterial infection could have contributed to the development of early CF lung disease. "Agents designed to remove permanent mucus covering airway surfaces of young children with CF appear to be rational strategies to prevent bacterial infection and disease progression," they concluded.

The study was supported by the National Heart, Lung, and Blood Institute; the North Carolina Translational and Clinical Sciences Institute; the National Health and Medical Research Council; and the Cystic Fibrosis Foundation. Two coauthors reported financial affiliations with Parion Sciences.

chestphysiciannews@chestnet.org

### VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** We have known for a long time that even healthy cystic fibrosis infants have inflammation in their lungs. More basic science research in mucin clearance is needed.

**SOURCE:** Esther CR et al. Sci Transl Med. 2019 Apr 3. doi: 10.1126/scitranslmed.aav3488.

# Maternal immunization protects infants from RSV

**BY BRUCE JANCIN**
*MDedge News*

LJUBLJANA, SLOVENIA – Passive protection of infants from severe respiratory syncytial virus lower respiratory tract infection during the first 6 months of life has convincingly been achieved through maternal immunization using a novel nanoparticle vaccine in the landmark PREPARE trial.

"I think it's important for everyone, especially people like myself who've been working on maternal immunization for about 20 years, to realize that this is a historic study," Flor M. Munoz, MD, declared in reporting the study results at the annual meeting of the European Society for Paediatric Infectious Diseases.

Bruce Jancin/MDedge News

**Dr. Flor M. Munoz**

"We have here for the first time a phase-3, global, randomized, placebo-controlled, observer-blinded clinical trial looking at an experimental vaccine in pregnant women for the protection of infants from a disease for which we really don't have other potential solutions quite yet, and in a period of high vulnerability," said Dr. Munoz, a pediatric infectious disease specialist at Baylor College of Medicine, Houston.

Indeed, respiratory syncytial virus (RSV) is the No. 2 cause of mortality worldwide during the first year of life. Moreover, most cases of severe RSV lower respiratory tract infection occur in otherwise healthy infants aged less than 5 months, when active immunization presents daunting challenges.

"While certainly mortality is uncommon in high-income countries, we do see significant hospitalization there due to severe RSV lower respiratory tract infection in the first year of life, sometimes more than other common diseases, like influenza," she noted.

PREPARE included 4,636 women with low-risk pregnancies who were randomized 2:1 to a single intramuscular injection of the investigational RSV vaccine or placebo during gestational weeks 28-36, with efficacy assessed through the first 180 days of life. The study took place at 87 sites in 11 countries during 4 years worth of RSV seasons. Roughly half of participants were South African, one-quarter were in the United States, and the rest were drawn from nine other low-, middle-, or high-income countries in the Northern and Southern Hemispheres. The median gestational age at vaccination was 32 weeks.

The primary efficacy endpoint specified by the Food and Drug Administration – but not other regulatory agencies – was the placebo-subtracted rate of RSV lower respiratory tract infection as defined by RSV detected by reverse transcription polymerase chain reaction, along with at least one clinical manifestation of lower respiratory tract infection, oxygen saturation below 95%, and/or tachypnea. The risk of this outcome was reduced by 39% during the first 90 days of life and by 27% through 180 days in infants in the maternal immunization group, a difference which didn't achieve statistical significance.

However, prespecified major secondary endpoints arguably of greater clinical relevance were consistently positive. Notably, maternal vaccination reduced infant hospitalization for RSV lower respiratory tract infection by 44% during the first 90 days of life, when levels of transplacentally transferred neutralizing antibodies against RSV A and B were highest, with events occurring in 57 of 2,765 evaluable infants in the active treatment arm and in 53 of 1,430 controls. Similarly, there was a 40% reduction through day 180. Moreover, rates of another key secondary endpoint – RSV lower respiratory tract infection plus severe hypoxemia with an oxygen saturation below 92% – were reduced by 48% and 42% through days 90 and 180, respectively. Thus, the vaccine's protective effect was greatest against the most severe outcomes of RSV infection in infancy, according to Dr. Munoz.

No safety signals related to this immunization strategy were seen during 1 year of follow-up of infants and 6 months for the mothers. Side effects were essentially limited to mild, self-limited injection site reactions, with zero impact on pregnancy and delivery.

An intriguing finding in an exploratory analysis was that the vaccine appeared to have ancillary benefits beyond prevention of medically significant RSV disease in the young infants. For example, the rate of all lower respiratory tract infections with severe hypoxemia – with no requirement for demonstration of RSV infection – was reduced by 46% during the first 90 days of life in the immunized group. Similarly, the rate of all-cause lower respiratory tract infection resulting in hospitalization was reduced by 28%.

"This is actually quite interesting, because these are unexpected benefits in terms of all-cause effects," the pediatrician commented, adding that she and her coinvestigators are delving into this phenomenon in order to gain better understanding.

Additional analyses of the recently completed PREPARE study are ongoing but already have yielded some important findings. For example, women immunized before 33 weeks' gestation had significantly greater transplacental antibody transfer than those immunized later in pregnancy, with resultant markedly greater vaccine efficacy in their offspring as well: a placebo-subtracted 70% reduction in RSV lower respiratory tract infection with severe hypoxemia through 90 days, compared with a 44% reduction associated with immunization at gestational week 33 or later. And when the interval between immunization and delivery was at least 30 days, the risk of this endpoint was reduced by 65%; in contrast, there was no significant difference between vaccine and placebo groups when time from immunization to delivery was less than 30 days.

Also noteworthy was that maternal immunization afforded no infant protection in the United States. This unanticipated finding is still under investigation, although suspicion centers around the fact that RSV seasons were generally milder there, and American women were vaccinated at a later gestational age, with a corresponding shorter interval to delivery.

The novel recombinant nanoparticle vaccine tested in PREPARE contains a nearly full-length RSV fusion protein produced in insect cells. The nanoparticles express both prefusion epitopes and epitopes common to pre- and postfusion conformations. Aluminum phosphate is employed as the adjuvant.

Novavax's stock price has been kicked to the curb since the company earlier reported that a large phase 3 trial of the vaccine failed to meet its primary endpoint for prevention of RSV lower respiratory tract infection in older adults. Now the vaccine's failure to meet its prespecified FDA-mandated primary endpoint in the maternal immunization study will doubtless spawn further financially dismissive headlines in the business press as well.

But pediatricians are famously advocates for children, and PREPARE received a warm welcome from the pediatric infectious disease community, regardless of investor response. Indeed, PREPARE was the only clinical trial deemed of sufficient import to be featured in the opening plenary session of ESPID 2019.

Ulrich Heininger, MD, professor of pediatrics at the University of Basel (Switzerland), who cochaired the session, jointly sponsored by ESPID and the Pediatric Infectious Diseases Society, declared, "These findings, I think, are a great step forward."

Dr. Munoz reported receiving research grants from Janssen, the National Institutes of Health, the Centers for Disease Control and Prevention, and Novavax, which sponsored the PREPARE trial, assisted by an $89 million grant from the Bill and Melinda Gates Foundation.

bjancin@mdedge.com

## VIEW ON THE NEWS

**Susan Millard, MD, FCCP, comments:** This is such an exciting trial! The risks of severe RSV infection, though, are often highest in extremely premature infants & premature infants with bronchopulmonary dysplasia (chronic lung disease of infancy) but in the trial, mothers got the placebo or the vaccine later in pregnancy. The vaccine would certainly help susceptible patient populations such as complex congenital heart disease infants born at term or close to term.

# ONCE-DAILY TRIPLE THERAPY


## TRELEGY SIMPLIFIES DELIVERY OF AN ICS, LABA, AND LAMA IN A SINGLE INHALER

- TRELEGY reduces exacerbations in patients with a history of COPD exacerbations

## INDICATION

TRELEGY is for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for reducing exacerbations in patients with a history of exacerbations. TRELEGY is NOT indicated for relief of acute bronchospasm or asthma.

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

- TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI), or any of the excipients.

### WARNINGS AND PRECAUTIONS

- TRELEGY is not for the treatment of asthma. LABA monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

**Please see additional Important Safety Information for TRELEGY throughout.**

**Please see Brief Summary of Prescribing Information for TRELEGY following this ad.**

COPD=chronic obstructive pulmonary disease; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

gsk | INNOVIVA

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

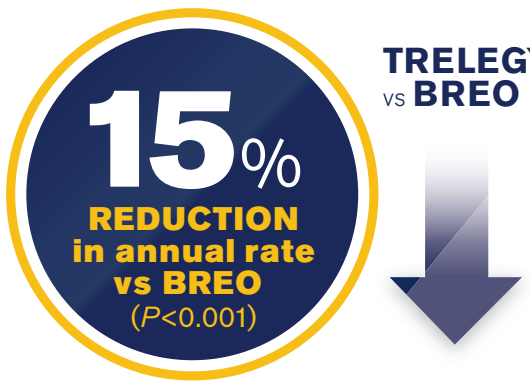
# TRELEGY: PROVEN EXACERBATION REDUCTION VS AN ICS/LABA AND VS A LAMA/LABA[1]

**IMPACT** *INFORMING THE PATHWAY OF COPD TREATMENT*

***PROVEN THE MOST EFFECTIVE TREATMENT VS ANORO AND VS BREO[1]***

In patients with a history of COPD exacerbations

**PRIMARY ENDPOINT:** Annual rate of moderate to severe exacerbations[1]




**TRELEGY 0.91** (n=4145)
vs **BREO 1.07** (n=4133)


**TRELEGY 0.91** (n=4145)
vs **ANORO 1.21** (n=2069)

**ANORO** is not approved for the reduction of COPD exacerbations.

## STUDY DESCRIPTION[1,2]

**Design:** A 12-month, randomized, double-blind, parallel-group study comparing the rate of moderate to severe exacerbations between TRELEGY and BREO 100/25 and between TRELEGY and ANORO 62.5/25, each delivered via the ELLIPTA inhaler. Patients were eligible if they were symptomatic with a postbronchodilator percent predicted $FEV_1$ <50% and a history of 1 or more moderate or severe exacerbations within the previous year, or with a postbronchodilator percent predicted $FEV_1$ of 50% to 80% and a history of 2 or more moderate exacerbations or 1 severe exacerbation in the previous year.

**Patients:** At screening, patients with COPD (N=10,355, mean age: 65 years) had a mean postbronchodilator percent predicted $FEV_1$ of 45.5% and a mean postbronchodilator $FEV_1$/FVC ratio: 0.47. Patients were randomized (2:2:1) to treatment following a 2-week run-in period on their current COPD treatment. Current medications included ICS + LABA + LAMA (34%), ICS + LABA (26%), LAMA + LABA (8%), LAMA (7%), and other (25%).

**Exacerbation severity criteria**: Moderate if treatment with systemic corticosteroids and/or antibiotics was required and severe if hospitalization was required.

$FEV_1$=forced expiratory volume in 1 second; FVC=forced vital capacity.

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

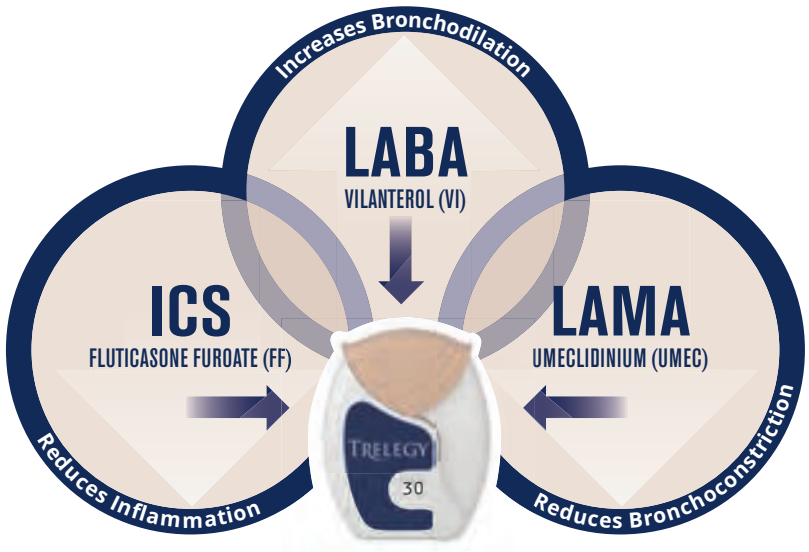
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.
- TRELEGY should not be used more often or at higher doses than recommended or with another LABA for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Advise patients to rinse their mouths with water without swallowing after inhalation.
- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as clinical features of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following use of ICS, like fluticasone furoate.
- 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.

**Please see additional Important Safety Information for TRELEGY throughout.**

**Please see Brief Summary of Prescribing Information for TRELEGY following this ad.**

# SIMPLIFIED DELIVERY OF TRIPLE THERAPY

***3 MEDICATIONS IN 1 INHALER WITH 1 DAILY INHALATION***




## According to GOLD 2019, use of multiple inhalers is one factor that may lead to poor inhaler technique[3w]

TRELEGY does not replace a rescue inhaler. Patients should be provided a short-acting beta$_2$-agonist, such as albuterol, to treat acute symptoms and instructed on how it should be used.

## See additional data. Visit DiscoverTRELEGY.com

### IMPORTANT SAFETY INFORMATION (cont'd)

**WARNINGS AND PRECAUTIONS (cont'd)**

- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of ICS in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, 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 TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY 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, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.


TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

SEE HOW TRELEGY MAY HELP YOUR APPROPRIATE PATIENTS. **SCAN THIS CODE.**

OR VISIT **DISCOVERTRELEGY.COM**

## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS (cont'd)

- Decreases in bone mineral density have been observed with long-term administration of products containing ICS. 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 (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of ICS or inhaled anticholinergics. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- 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.

### ADVERSE REACTIONS

- The most common adverse reactions (≥1% and more common than placebo + FF/VI) reported in two 12-week clinical trials with UMEC + FF/VI, the components of TRELEGY, (and placebo + FF/VI) were: headache, 4% (3%); back pain, 4% (2%); dysgeusia, 2% (<1%); diarrhea, 2% (<1%); cough, 1% (<1%); oropharyngeal pain, 1% (0%); and gastroenteritis, 1% (0%).
- Additional adverse reactions (≥1% incidence) reported in subjects taking TRELEGY in a 52-week trial included upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

### DRUG INTERACTIONS

- TRELEGY 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 they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution, as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of TRELEGY with other anticholinergic-containing drugs, as this may lead to an increase in anticholinergic adverse effects.

### USE IN SPECIFIC POPULATIONS

- Use TRELEGY with caution in patients with moderate or severe hepatic impairment, as fluticasone furoate systemic exposure may increase by up to 3-fold. Monitor for corticosteroid-related side effects.

**Please see additional Important Safety Information for TRELEGY throughout.**

**Please see Brief Summary of full Prescribing Information for TRELEGY following this ad.**

**References: 1.** Lipson DA, Barnhart F, Brealy N, et al; for the IMPACT Investigators. Once-daily single-inhaler triple vs dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. **2.** Data on file, GSK. **3.** Global Initiative for Chronic Obstructive Lung Disease (GOLD): *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.* 2019 report. www.goldcopd.org. Accessed January 18, 2019.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA


FVUJRNA190002 April 2019
Produced in USA.

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

## BRIEF SUMMARY

**TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation**

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

## 1 INDICATIONS AND USAGE

TRELEGY is indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. TRELEGY is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use

TRELEGY is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

## 4 CONTRAINDICATIONS

The use of TRELEGY is contraindicated in the following conditions: severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11) of full prescribing information]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

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

Use of long-acting beta$_2$-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

Available data from clinical trials in subjects with COPD do not suggest an increased risk of death with use of LABA in patients with COPD.

### 5.2 Deterioration of Disease and Acute Episodes

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

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

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 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.

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

### 5.3 Excessive Use of TRELEGY and Use With Other Long-acting Beta$_2$-agonists

TRELEGY 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 TRELEGY should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

### 5.4 Local Effects of Inhaled Corticosteroids

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

### 5.5 Pneumonia

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

In two 12-week studies of subjects with COPD (N=824), the incidence of pneumonia was <1% for both treatment arms: umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg. Fatal pneumonia occurred in 1 subject receiving placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg.

In a 52-week trial of subjects with COPD (N=10,355), the incidence of pneumonia was 8% for TRELEGY (n=4,151), 7% for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 5% for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Fatal pneumonia occurred in 12 of 4,151 patients (0.35 per 100 patient-years) receiving TRELEGY, 5 of 4,134 patients (0.17 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (0.29 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 9 subjects receiving placebo, 10 subjects receiving fluticasone furoate 100 mcg, and 6 subjects receiving vilanterol 25 mcg (<0.2 per 100 patient-years for each treatment group).

### 5.6 Immunosuppression

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

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

### 5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [$FEV_1$]), beta-agonist use, and COPD 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 TRELEGY may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (eg, rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

*Continued on next page*

### 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 fluticasone furoate in TRELEGY. 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 TRELEGY 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, appropriate therapy should be considered.

### 5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

### 5.10 Paradoxical Bronchospasm

As with other inhaled medicines, TRELEGY can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with TRELEGY, it should be treated immediately with an inhaled, short-acting bronchodilator; TRELEGY 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 TRELEGY. Discontinue TRELEGY 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 TRELEGY *[see Contraindications (4)]*.

### 5.12 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY 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 *[see Clinical Pharmacology (12.2) of full prescribing information]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

TRELEGY, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction (MI), non-fatal acute MI, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for TRELEGY (n=4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 2.2 per 100 patient-years for umeclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving TRELEGY, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving umeclidinium/vilanterol.

In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,568 subjects with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg, 86 subjects receiving placebo, 80 subjects receiving fluticasone furoate 100 mcg, and 90 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

### 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 (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating TRELEGY and periodically thereafter. If significant reductions in BMD are seen and TRELEGY is still considered medically important for that patient's COPD therapy, use of medicine to treat or prevent osteoporosis should be strongly considered.

### 5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (eg, 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 healthcare provider immediately if any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.

### 5.15 Worsening of Urinary Retention

TRELEGY, like all medicines containing an anticholinergic, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop.

### 5.16 Coexisting Conditions

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

### 5.17 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.

## 6 ADVERSE REACTIONS

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

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1)]*
- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular effects *[see Warnings and Precautions (5.12)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.14)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.15)]*

### 6.1 Clinical Trials Experience

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

The safety of TRELEGY is based on the safety data from two 12-week treatment trials with the coadministration of umeclidinium and the fixed-dose combination fluticasone furoate/vilanterol and a 52-week long-term trial of TRELEGY compared with the fixed-dose combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol *[see Clinical Studies (14)]*.

Trials 1 and 2

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umeclidinium + fluticasone furoate/vilanterol, the components of TRELEGY, compared with placebo + fluticasone furoate/vilanterol. A total of 824 subjects with COPD across two 12-week, randomized, double-blind clinical trials received at least 1 dose of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol
100 mcg/25 mcg or placebo + fluticasone furoate/vilanterol 100 mcg/25 mcg administered once daily (mean age: 64 years; 92% white, 66% male across all treatments) *[see Clinical Studies (14) of full prescribing information]*. The incidence of adverse reactions associated with the use of umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg presented in Table 1 is based on the two 12-week trials.

*Continued on next page*

**Table 1. Adverse Reactions With Umeclidinium + Fluticasone Furoate/Vilanterol With ≥1% Incidence and More Common Than Placebo + Fluticasone Furoate/Vilanterol (Trials 1 and 2)**

| Adverse Reaction | Umeclidinium + Fluticasone Furoate/ Vilanterol (n=412) % | Placebo + Fluticasone Furoate/ Vilanterol (n=412) % |
|---|---|---|
| Nervous system disorders | | |
| Headache | 4 | 3 |
| Dysgeusia | 2 | <1 |
| Musculoskeletal and connective tissue disorders | | |
| Back pain | 4 | 2 |
| Respiratory, thoracic, and mediastinal disorders | | |
| Cough | 1 | <1 |
| Oropharyngeal pain | 1 | 0 |
| Gastrointestinal disorders | | |
| Diarrhea | 2 | <1 |
| Infections and infestations | | |
| Gastroenteritis | 1 | 0 |

Trial 3 - Long-term Safety Data

A 52-week trial (Trial 3) evaluated the long-term safety of TRELEGY compared with the fixed-dose combinations of fluticasone furoate/vilanterol 100 mcg/25 mcg and umeclidinium/vilanterol 62.5 mcg/25 mcg. A total of 10,355 subjects with COPD with a history of moderate or severe exacerbations within the prior 12 months were randomized (2:2:1) to receive TRELEGY, fluticasone furoate/vilanterol, or umeclidinium/vilanterol administered once daily in a double-blind clinical trial (mean age: 65 years, 77% white, 66% male across all treatments) *[see Clinical Studies (14)]*.

The incidence of adverse reactions in the long-term trial were consistent with those in Trials 1 and 2. However, in addition to the adverse reactions shown in Table 1, adverse reactions occurring in ≥1% of the subjects treated with TRELEGY (n=4,151) for up to 52 weeks also included upper respiratory tract infection, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, oral candidiasis *[see Warnings and Precautions (5.4)]*, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, constipation, urinary tract infection, and dysphonia.

## 7 DRUG INTERACTIONS

### 7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are 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 TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

### 7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

### 7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

### 7.4 Non–Potassium-Sparing Diuretics

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

### 7.5 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRELEGY with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.14, 5.15)]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are insufficient data on the use of TRELEGY or its individual components, fluticasone furoate, umeclidinium, and vilanterol, in pregnant women to inform a drug-associated risk.

Clinical Considerations

*Labor and Delivery:* TRELEGY should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

### 8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRELEGY and any potential adverse effects on the breastfed child from fluticasone furoate, umeclidinium, or vilanterol, or from the underlying maternal condition.

### 8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. In Trial 3, 2,265 subjects aged 65 years and older, of which 565 subjects were aged 75 years and older, were administered TRELEGY. 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

TRELEGY has not been studied in subjects with hepatic impairment. Information on the individual components is provided below.

Fluticasone Furoate/Vilanterol

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. Monitor patients for corticosteroid-related side effects *[see Clinical Pharmacology (12.3) of full prescribing information]*.

Umeclidinium

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in $C_{max}$ or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls.

Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full prescribing information]*.

## 10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

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

### 10.1 Fluticasone Furoate

Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 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 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

### 10.3 Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (eg, 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 (Patient Information and Instructions for Use *of full prescribing information*).

Not for Acute Symptoms

Inform patients that TRELEGY is not meant to relieve acute symptoms of COPD, and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled,

*Continued on next page*

**BRIEF SUMMARY**

**TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation** *(cont'd)*

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 TRELEGY 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.

Local Effects

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

Pneumonia

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

Immunosuppression

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

Hypercorticism and Adrenal Suppression

Advise patients that TRELEGY 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 TRELEGY.

Paradoxical Bronchospasm

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

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY 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 TRELEGY.

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.

Glaucoma and Cataracts

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

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

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (eg, difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develop.

Risks Associated With Beta-agonist Therapy

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



TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 01/2019 TRL:4BRS


TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

Trademarks are owned by or licensed to the GSK group of companies.


FVUJRNA190002 April 2019
Produced in USA.

TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)

# Interaction of sleep and opioid use disorder is complex

**BY KARI OAKES**
*MDedge News*

MILWAUKEE – Individuals with chronic pain frequently have disrupted sleep and also may be at risk for opioid use disorder. However, even with advanced monitoring, it's not clear how sleep modulates pain and opioid cravings.

Sleep has an impact on positive and negative affect, but new research shows that the link between sleep and mood states that may contribute to opioid use disorder is not straightforward. At the scientific meeting of the American Pain Society, Patrick Finan, PhD, of Johns Hopkins University, Baltimore, discussed how sleep and mood affect cravings for opioids among those in treatment for opioid use disorder (OUD).

Affective function, mesolimbic system function, and pain modulation are all adversely affected by poor sleep, said Dr. Finan, who told attendees that one key question he and his colleagues were seeking to answer was whether those with OUD and chronic pain had more disturbed sleep than those with OUD alone. Also, the researchers wanted to know whether the ups and downs of sleep on a day-to-day basis were reflected in pain scores among those with OUD, as would be predicted by prevailing models.

Finally, two "proximal indicators" of relapse risk, affect, and heroin craving, might be affected by both sleep and pain, and Dr. Finan and collaborators sought to explore that association.

The work was part of a larger study looking at the natural history of OUD and OUD with comorbid chronic pain. To participate in this parent study, adults with OUD had to be seeking treatment or currently enrolled in methadone or buprenorphine maintenance treatment, and without current major depressive disorder. Also, patients could not have a history of significant mental illness, cognitive impairment, or a medical condition that would interfere with study participation. A total of 56 patients participated, and 20 of these individuals also had chronic pain.

Those with OUD and chronic pain qualified if they had pain (not related to opioid withdrawal) averaging above 3 on a 0-10 pain rating scale over the past week; additional criteria included pain for at least the past 3 months, with 10 or more days per month of pain.

Pain ratings were captured via a smartphone app that prompted participants to enter a pain rating at three random times during each day. Each evening, patients also completed a sleep diary giving information about bedtime, sleep-onset latency, waking after sleep onset, and wake time for the preceding day.

A self-applied ambulatory electroencephalogram applied to the forehead was used for up to 7 consecutive nights to capture sleep continuity estimates; the device has been validated against polysomnography data in other work. Participants were given incentives to use the device, and this "yielded strong adherence," with an average of 5 nights of use per participant, Dr. Finan said.

Patients were an average age of about 49 years, and were 75% male. African American participants made up just over half of the cohort, and 43% were white. Participants were roughly evenly divided in the type of maintenance therapy they were taking. Overall, 39% of participants had a positive urine toxicology screen.

For patients with chronic pain, 45% of all momentary pain reports had a pain score over zero, with a mean of 32 days of pain. Looking at the data another way, Dr. Finan said, 58% of all patient-days had at least one momentary report of pain greater than zero. On average, participants recorded a pain score of 2.27.

Brief Pain Inventory scores at baseline showed a mean severity of 5, and a pain interference score of 5.07.

Participants with OUD and chronic pain did not differ across any EEG-recorded sleep measures, compared with those with OUD alone. However, subjective reports of sleep were actually better overall for those with chronic pain than the objective EEG reports. The EEG recordings captured an average of 9.11 minutes more of waking after sleep onset ($P$ less than .001). Also, total sleep time was 10.37 minutes shorter as recorded by the EEG than by self-report ($P$ less than .001). Overall sleep efficiency was also worse by 5.96 minutes according to the EEG, compared with self-report ($P$ less than .001).

"Sleep is objectively poor but subjectively 'normal' and variable in opioid use disorder patients," Dr. Finan said. In aggregate, however, neither diary-based subjective nor EEG-based objective sleep measures differed between those with and without chronic pain in the research cohort. This phenomenon of sleep efficiency being self-reported as higher than objective measures capture sleep has also been seen in those newly abstinent from cocaine, Dr. Finan said, adding that it's possible individuals with substance use disorder who are new to treatment simply feel better than they have in some time along many dimensions, with sleep being one such domain.

Pain on a given day didn't predict poor sleep on that night, except that sleep onset took slightly longer ($P$ = .01), said Dr. Finan. He noted that "there was no substantive effect on other sleep continuity parameters." Looking at how negative affect mediated craving for heroin, Dr. Finan and colleagues found that negative affect–related craving was significantly greater for those with chronic pain ($P$ less than .001).

Unlike findings in patients without OUD, having disrupted sleep continuity was more associated with increased daily negative affect, rather than decreased positive affect. And this increased negative affect was associated with heroin cravings, said Dr. Finan. "In the past few years, we've seen quite a few studies that have found some abnormalities in the reward system in patients with chronic pain." Whether poor sleep is a mediator of these abnormalities deserves further study.

The study was supported by the National Institutes of Health. Dr. Finan reported no outside sources of funding.

koakes@mdedge.com

Mladen Zivkovic/iStock/Getty Images

# Trial finds no link between CPAP and weight gain

**BY ANDREW D. BOWSER**
*MDedge News*

**FROM THE JOURNAL *CHEST*®** ▪ Continuous positive airway pressure (CPAP) over several years did not lead to clinically concerning levels of weight gain among patients with obstructive sleep apnea and comorbid cardiovascular disease enrolled in a large international trial, findings from a large, multicenter trial show.

No differences in weight, body mass index, or other body measurements were found when comparing CPAP and control groups in a post hoc analysis of the Sleep Apnea Cardiovascular Endpoints (SAVE) trial, which included 2,483 adults enrolled at 89 centers in seven countries.

COURTESY RESMED

In a subanalysis, there was a small but statistically significant weight gain of less than 400 g in men who used CPAP at least 4 hours per night as compared to matched controls. However, there were no differences in BMI or neck and waist circumferences for these men, and no such changes were observed in women, according to the investigators, led by Qiong Ou, MD, of Guangdong (China) General Hospital and R. Doug McEvoy, MD, of the Adelaide Institute for Sleep Health at Flinders University, Adelaide, Australia.

"Such a small change in weight, even with good adherence over several years, is highly unlikely to have any serious clinical ramifications," wrote the investigators of the study published in Chest.

"Taken together, these results indicate that long-term CPAP treatment is unlikely to exacerbate the problems of overweight and obesity that are common among patients with OSA," they added.

In a previous meta-analysis of randomized trials, investigators concluded that CPAP promoted significant increases in BMI and weight. However, the median study duration was only 3 months.

In contrast, the analysis of the SAVE trial included adults who had regular body measurements over a mean follow-up of nearly 4 years.

That long-term follow-up provided an "ideal opportunity" to assess whether CPAP treatment promotes weight gain in OSA patients over the course of several years, the authors of the SAVE trial analysis wrote.

For men in the SAVE trial, the difference in weight change for the CPAP group vs. the control group was just 0.07 kg (95% confidence interval, –0.40 to 0.54; $P = .773$) while in women, the difference for CPAP vs. controls was –0.14 kg (95% CI, –0.37 to 0.09; $P = .233$), the investigators reported.

Weight gain was significantly higher among men with good CPAP adherence, defined as use for at least 4 hours per night, investigators said, noting a mean difference of 0.38 kg (95% CI, 0.04-0.73; $P = .031$), though no other differences were found in body measurements for men, and no such associations were found in women with good CPAP adherence.

It's not exactly clear why this SAVE analysis would find no evidence of CPAP promoting weight gain over the long term, in contrast to the earlier meta-analysis of short-term studies finding a significant risk of weight gain.

However, it is possible that differences in study populations such as ethnicity, age, or comorbidities contributed to the differences, said investigators.

For example, results of regression analysis in the present study showed that, compared with recruitment in Australia, recruitment in China and India was significantly linked to weight loss, while recruitment in New Zealand was linked to weight gain.

Dr. Ou had no disclosures related to the study, while Dr. McEvoy reported disclosures related to Philips Respironics, ResMed, Fisher & Paykel, Air Liquide, and the National Health and Medical Research Council of Australia.

chestphysiciannews@chestnet.org

**SOURCE:** Ou Q et al. Chest. 2019 Apr;155(4):720-9.



# Insomnia meds get boxed warning from FDA

**BY CHRISTOPHER PALMER**
*MDedge News*

The Food and Drug Administration will now require that certain medications prescribed for insomnia carry a boxed warning because of associated complex sleep behaviors.

These behaviors, including sleep walking, sleep driving, and engaging in other activities while not fully awake, are more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than they are with other prescription medicines used for sleep. Although these complex sleep behaviors are rare, they are potentially very dangerous. Boxed warnings are the FDA's most prominent warning, but the agency will also require a contraindication – its strongest warning – to avoid use in patients who've previously experienced these behaviors with any of these medications.

FDA NEWS

Complex sleep behaviors have been seen with these medications in patients with and without a history of them, at low doses, and even after one dose of the medication. They've also been observed with and without concomitant use of alcohol or other CNS depressants.

Health care professionals should advise patients about these risks, even though they are rare. Patients should contact health care professionals if they either experience a complex sleep behavior while not fully awake on one of these medicines or have performed activities they don't remember while taking the medicine.

More information about these risks and the safety warnings can be found in the FDA's safety announcement. Other information is also available in a press announcement from the agency.

cpalmer@mdedge.com

# Insomnia correlated with epilepsy seizure frequency

**BY JAKE REMALY**
*MDedge News*

**Dr. Thapanee Somboon**

PHILADELPHIA – Nearly a quarter of adults with epilepsy have moderate or severe insomnia, and insomnia symptoms are associated with depression, anxiety, worse seizure control, and poorer quality of life, according to a prospective analysis presented at the annual meeting of the American Academy of Neurology. Insomnia symptoms are not associated with epilepsy type, number of antiepileptic drugs (AEDs), or AED standardized dose, however.

"Given the potential benefits of sleep therapies on epilepsy outcomes, routine screening of insomnia symptoms is warranted," said lead study author Thapanee Somboon, MD, a researcher at the sleep disorders center at Cleveland Clinic Neurological Institute and at Prasat Neurological Institute in Bangkok.

Insomnia is common and associated with depression in patients with epilepsy, but prior studies that looked at the relationship between insomnia and epilepsy-related characteristics yielded limited and conflicting results, according to Dr. Somboon.

To evaluate potential associations between insomnia and epilepsy, Dr. Somboon and colleagues conducted a prospective analysis of data from 270 patients with epilepsy who presented to the Cleveland Clinic Epilepsy Center for an initial evaluation between January and August 2018. The patients completed the Insomnia Severity Index (ISI). An ISI score of 8 or greater indicated clinical insomnia symptoms, and an ISI score of 15 or greater indicated moderate or severe insomnia symptoms.

*"Given the potential benefits of sleep therapies on epilepsy outcomes, routine screening of insomnia symptoms is warranted."*

The researchers used Spearman's correlation and the Kruskal-Wallis test to evaluate associations among insomnia symptoms and AED standardized dose, monthly seizure frequency, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder Questionnaire (GAD-7), and Quality of Life in Epilepsy-10 (QOLIE10).

DEMAERRE/GETTY IMAGES

Among the 270 patients, the average age was 43.5 years, 58% were female, 74% had focal epilepsy, and 26% had one or more seizures per month. The population's median ISI score was 7. Nearly half had an ISI score of 8 or greater, and 23% had an ISI score of 15 or greater.

"A positive correlation was found between ISI and PHQ-9 ($r = 0.64$, $P$ less than .001), GAD-7 ($r = 0.68$, $P$ less than .001), QOLIE ($r = 0.55$, $P$ less than .001), and monthly seizure frequency ($r = 0.31$, $P$ less than .001)," the researchers reported. Insomnia symptoms had a significantly stronger correlation with PHQ-9 and GAD-7 than with seizure frequency.

Dr. Somboon had no disclosures. A coinvestigator has received research support from Jazz Pharmaceuticals.

jremaly@mdedge.com

**SOURCE:** Somboon T et al. AAN 2019, Abstract P3.6-026.

# Shared decision-making in action: Real data on biopsy risk and how to mitigate it

BY MATT ABOUDARA, MD, FCCP

In a study highlighted in a recent issue of *CHEST Physician*, Hou and colleagues analyzed complications from biopsies of lung abnormalities seen on CT scans by conducting a large retrospective study with data gleaned from national databases of patients undergoing CT-guided biopsy, surgery, or bronchoscopy.[1] While it should not be interpreted as representative of a lung cancer screening population (for excellent comments by Drs. Rivera and Silvestri regarding the study, see: https://tinyurl.com/y52ucb94), it does raises two important questions when performing shared decision-making for low dose CT (LDCT) scanning: (1) What information should clinicians discuss with patients regarding various biopsy methods until more data are available? (2) How do we mitigate complications from biopsies?

While procedure-specific biopsy risk may be generalizable, it may be institutionally specific, and knowledge of local skill and outcomes data can help guide discussions. With that said, some general information can inform decisions. The NAVIGATE study investigators recently published their 1-year follow-up results using a navigational bronchoscopy system (superDimension™). While inherent limitations to this study exist, it does provide some useful information as to procedure-related complications from a large sample of patients who approximate a lung cancer screening population. This group was composed of both academic and community centers and prospectively followed 1,215 patients for 1 year.[2] The average age of the population was 67.6 (± 11.3), and 80% were current or former smokers. The median nodule size was 2 cm. The diagnostic yield was 73% at 1 year follow-up (data will be re-analyzed at 2 years). The pneumothorax rate was 4%, with 3% requiring chest tube. Hemorrhage occurred in 2.5% of all patients, with 1.5% having a common terminology criteria for adverse events (CTCAE) ≥ 2. Grade 4 respiratory failure occurred in 1 patient. There were no ENB procedure-related deaths. It should be noted that individuals performing these procedures were, by and large, high-volume and experienced users.

In comparison, the overall pooled sensitivity for CT scan-guided biopsy is 90% for pulmonary nodules and masses. The yield is lower, however, for smaller lesions (≤2.0) and ranges from 74% to 77%.[3] The average pneumothorax rate is 20%, with 1% to 3% requiring chest tube placement. Risk factors for pneumothorax vary between studies, but, generally speaking, have been associated with nodules ≤ 2 cm, those within 2 cm of the pleura (but not abutting the pleura), and emphysema in the track of needle trajectory. Pulmonary hemorrhage occurs 30% of the time but is mild in most cases. Hemoptysis and severe hemorrhage occur at rates of 4% and <1%, respectively. Risk factors for development of pulmonary hemorrhage include small lesion size (< 2 cm) and lesions > 2 cm from the pleura.

When considering surgical lung biopsies and resection, recent data suggest every effort should be made to encourage smoking cessation in order to mitigate postoperative morbidity. In a retrospective study by Fukui and colleagues,[4] respiratory morbidity (defined as hypoxia, pneumonia, atelectasis, and uncontrolled sputum production) was 22% in smokers vs 3.5% in never smokers. The rate of complications decreased as the time from smoking cessation to date of surgery increased.

The goal for each patient who is counseled should be to limit the number of procedures and achieve the greatest diagnostic confidence with the lowest complication rate. With these risks and diagnostic yield in mind, the decision to recommend a particular biopsy strategy (or no biopsy at all) should be based on current guideline recommendations: (1) patient co-morbidities and preferences; (2) size of index nodule or mass; (3) presence of pathologically enlarged mediastinal and/or hilar lymphadenopathy; (4) evidence of extrathoracic metastasis; and (5) institutional expertise. Specifically speaking for the pulmonologist, this translates into identifying specific procedural "champions" who are dedicated to performing these procedures and are members of a multidisciplinary thoracic team. These individuals should have dedicated training in advanced diagnostic procedures to achieve the aforementioned goals.[5] The same should hold true for transthoracic, CT-guided biopsies. Interventional pulmonology fellowships are structured to provide exposure to multidisciplinary nodule clinics and tumor boards, establishing quality improvement initiatives, as well as developing procedural expertise.[6]

It is apparent that shared decision-making can become complex. These details will likely be lost to a primary care provider simply due to time constraints and information overload. As such, pulmonologists should be at the forefront of lung cancer screening – in programmatic development, implementation, and providing education to providers directly involved with shared decision-making discussions.

*Dr. Aboudara is with the Division of Allergy, Pulmonary, and Critical Care; Vanderbilt University Medical Center; Nashville, Tennessee.*

## References

1. Huo J, Xu Y, Sheu T, et al. Complication rates and downstream medical costs associated with invasive diagnostic procedures for lung abnormalities in the community setting: Complications and medical costs associated with diagnostic procedures for lung abnormalities. *JAMA Intern Med*. 2019;179:324-32.

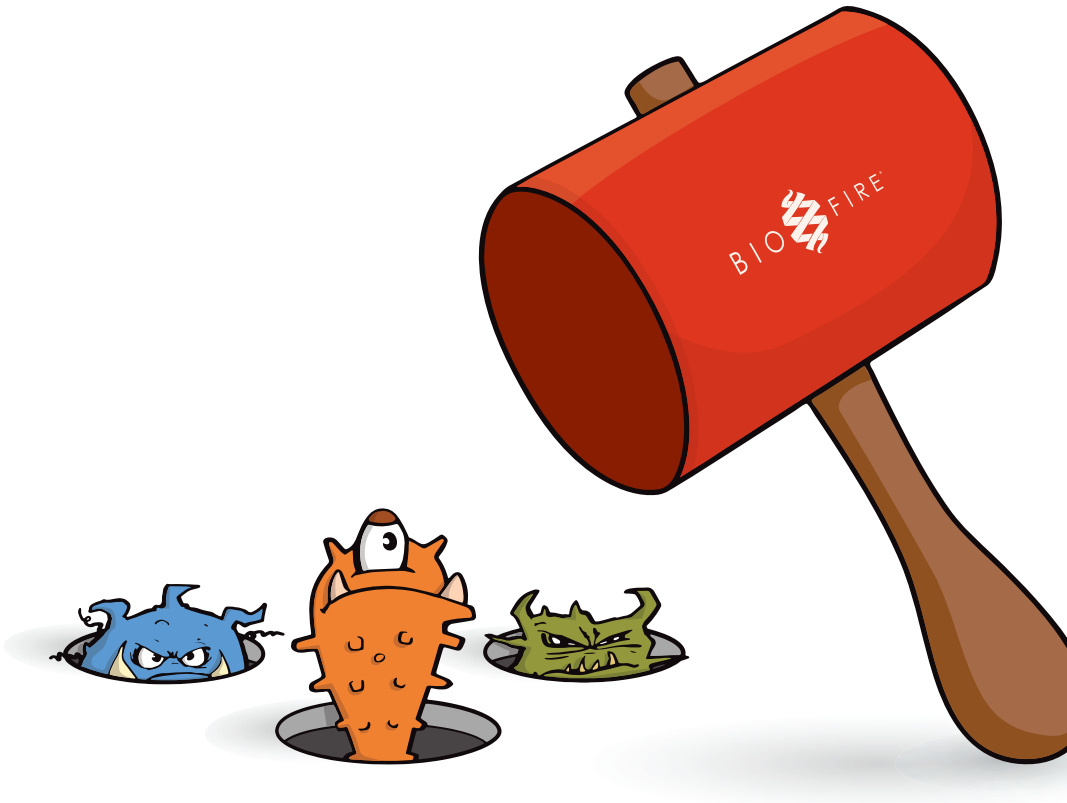
2. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: One-year results of the prospective, multicenter NAVIGATE study. *J Thorac Oncol.* 2019;14(3):445-58.

3. Ohno Y, Hatabu H, Takenaka D, et al. CT-guided transthoracic needle aspiration biopsy of small (< or = 20 mm) solitary pulmonary nodules. *AJR Am J Roentgenol.* 2003;180(6):1665-69.

4. Fukui M, Suzuki K, Matsunaga T, et al. Importance of smoking cessation on surgical outcome in primary lung cancer. *Ann Thorac Surg.* 2019;107(4):1005-09.

5. Mahajan A, Khandhar S, Folch EE. Pulmonary Perspectives®: Ensuring quality for EBUS bronchoscopy with varying levels of practitioner experience. *CHEST Physician*. April 6, 2017. https://tinyurl.com/y3hwlc4g. .

6. Mullon JJ, Burkart KM, Silvestri G, et al. Interventional Pulmonology Fellowship Accreditation Standards: Executive summary of the Multisociety Interventional Pulmonology Fellowship Accreditation Committee. *Chest.* 2017;151(5):1114-21.




# Timing is critical.

## Improve critical care diagnosis with syndromic infectious disease testing from BioFire.

High-acuity patients require time-sensitive, specialized care. As a critical care physician, you need rapid, reliable test results to make informed intervention decisions. The BioFire® FilmArray® System utilizes a syndromic approach—simultaneously testing for different pathogens that can cause similar symptoms—to deliver actionable results in about an hour. BioFire helps you quickly identify specific infectious agents, allowing you to begin targeted treatment sooner.

Fast: Rapid turnaround time facilitates efficient diagnosis and treatment decisions.

Accurate: Superior sensitivity and specificity for results you can trust.

Comprehensive: One test to check for a broad spectrum of pathogens—viruses, bacteria, parasites, fungi, and antimicrobial resistance genes—so you can determine the best course of action in the shortest amount of time.

Learn more about solutions from the leader in syndromic testing at **biofiredx.com**.

### BioFire® FilmArray® Panels

Tests available for your lab:

**Respiratory**
1 Test / 21 Targets / 45 Minutes

**Blood Culture Identification**
1 Test / 27 Targets / 1 Hour

**Gastrointestinal**
1 Test / 22 Targets / 1 Hour

**Meningitis/Encephalitis**
1 Test / 14 Targets / 1 Hour

**Pneumonia**
1 Test / 33 Targets / 1 Hour

BIOFIRE®
A BIOMÉRIEUX COMPANY

**Syndromic Testing: The Right Test, The First Time.**

BFDX-MKT-0197-02

# Addressing current asthma management: What clinicians told us

*A Medscape/CHEST Survey*

BY MEGAN BROOKS

There are differences in how pulmonologists and other clinicians approach the diagnosis and management of patients with moderate to severe asthma, according to a survey conducted by Medscape in collaboration with CHEST, the American College of Chest Physicians. Despite some of these differences, those surveyed do predominantly favor similar treatment options, including inhaled corticosteroids and biologics. Biologics in particular are perceived as a promising therapeutic approach for moderate to severe asthma by clinicians overall, and many are also comfortable prescribing them.

Medscape and CHEST asked 763 clinicians about their views on moderate to severe asthma. Responses came from 100 pulmonologists; 102 allergists/immunologists; 102 critical care medicine physicians; 100 emergency medicine (EM) physicians; 104 pediatricians; 100 primary care physicians (PCPs); and 155 nurse practitioners (NPs), physician assistants (PAs), or registered nurses (RNs).

## Inhaled steroids top treatment choice

Survey respondents ranked an inhaled corticosteroid with a long-acting bronchodilator as the favored medication for patients with moderate to severe asthma; 83% of allergists/immunologists feel this way, as do between 52% and 63% of the other clinicians, including pulmonologists.

Inhaled corticosteroids alone are generally preferred by 23%-28% of clinicians surveyed, with the exception of allergists/immunologists (12%). EM physicians (19%) and pediatricians (16%) tend to more often favor an inhaled corticosteroid and leukotriene-modifying agent than do other clinicians, but notably, none of the allergists/immunologists felt this way.

## Biologics are an important step forward

When it comes to biologic agents for moderate to severe asthma, it is allergists/immunologists (91%) who say they are most comfortable prescribing them. This percentage drops to 59% for pulmonologists, 34% for NP/PA/RNs, 20% for critical care medicine physicians, 16% for PCPs, 7% for pediatricians, and just 2% of EM physicians.

Aaron B. Holley, MD, FCCP, program director at the Pulmonary and Critical Care Medical Fellowship, Department of Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland, and a member of the Moderate to Severe Asthma Center of Excellence steering committee, noted that the latest rage is to personalize treatment by "phenotyping" asthma, with the thought being that certain asthma phenotypes will respond well to some treatments, but not to others. "This sounds good in academic and scientific papers, but remains difficult to operationalize in the clinic," said Holley.

He also noted that the new biologics all target one specific phenotype: eosinophilic asthma. "This phenotype makes up approximately 50% of all patients with asthma; however, the other 50% have no targeted treatments available, and they don't necessarily respond well to conventional inhaler therapy," said Holley.

And for patients with severe, poorly responsive asthma, it's hard to say precisely what percentage is being treated inappropriately for their phenotype, versus what percentage is noncompliant, versus what percentage is due to socioeconomic status and behavioral health issues, he noted.

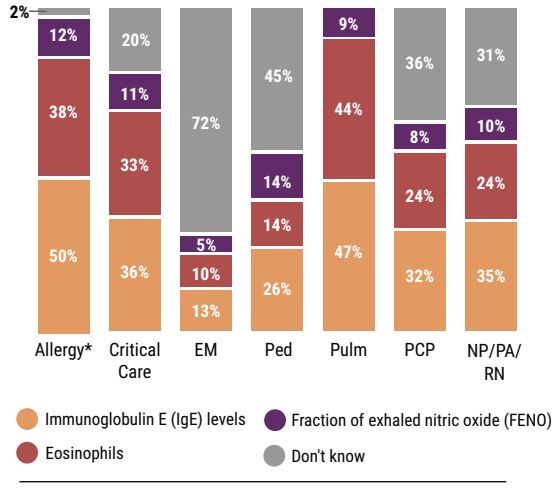
The solution? "There is no easy solution," said Holley. "More specialized, severe asthma clinics? Greater education on inhaler use and disease severity? Concomitant management of behavioral health complaints? All these are necessary, but they're also resource-intensive."

Still, in his view, the glass is half-full. "The biologics are an important step forward, and we're getting better at phenotyping. Compared with 5-10 years ago, we're in a much better place."

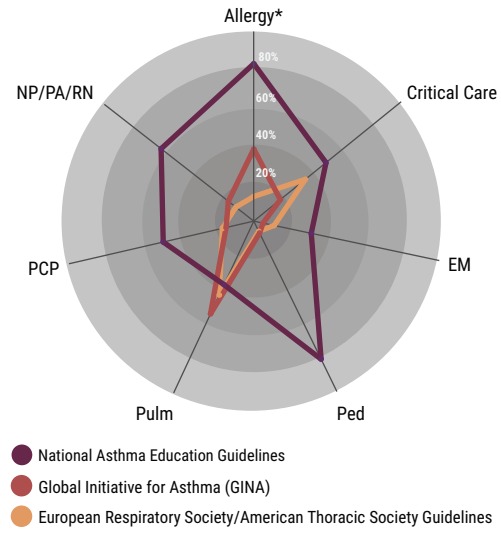
*When it comes to biologic agents for moderate to severe asthma, it is allergists/immunologists (91%) who say they are most comfortable prescribing them. This percentage drops to 59% for pulmonologists, 34% for NP/PA/RNs, 20% for critical care medicine physicians, 16% for PCPs, 7% for pediatricians, and just 2% of EM physicians.*

## Medscape/CHEST Survey

### Biomarkers for Moderate to Severe Asthma Considered Most Important Among Clinicians

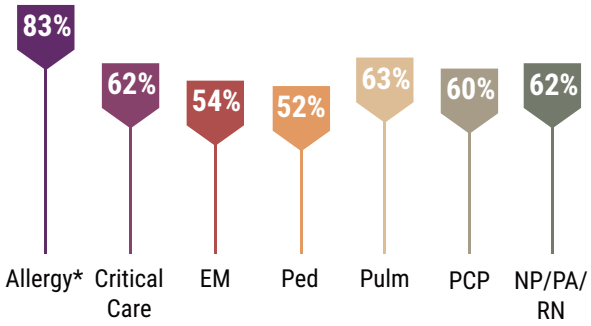



### Use of Asthma Evaluation Guidelines

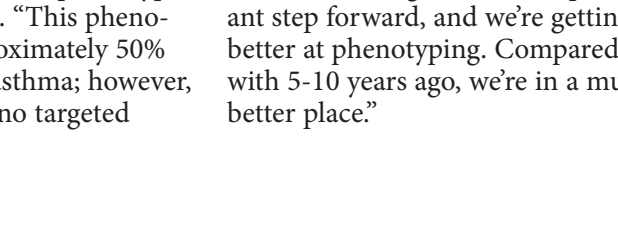



### Inhaled Corticosteroid With Long-Acting Bronchodilator Favored as Treatment

Percentage of Specialists Ranking This Medication As #1




### Clinicians Comfortable With Prescribing Biologics




*Includes allergy and immunology

Source: Medscape/CHEST Survey of 763 clinicians; August 29 to October 11, 2018.

## Preferred biomarkers

Familiarity with biomarkers for moderate or severe asthma is universal among pulmonologists. Only 2% of allergists/immunologists are not familiar with biomarkers, compared with nearly three quarters of EM physicians, 45% of pediatricians, 36% of PCPs, 31% of NP/PA/RNs, and 20% of critical care medicine physicians.

Immunoglobulin E (IgE) levels ranked as the most important biomarker for moderate or severe asthma, favored by 47% of pulmonologists and 50% of allergists/immunologists, followed by eosinophils, preferred by 44% of pulmonologists and 38% of allergists/immunologists. Between 26% and 36% of other clinicians rank IgE tops, except for EM physicians (13%). About one third of critical care medicine physicians and one quarter of PCPs and NP/PA/RNs think eosinophils are the most important biomarker, compared with only 14% of pediatricians and 10% of EM physicians.

Fraction of exhaled nitric oxide (FeNO) is least favored by all clinicians surveyed. Just 9% of pulmonologists, 12% of allergists/immunologists, and 5% of EM physicians like this biomarker. Pediatricians ranked FeNO the highest among those surveyed, but only at 14%.

## Assessment tools and guidelines

One "interesting" finding is the difference between specialties in use of the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ), commented Holley. Most pulmonologists (57%) and allergists/immunologists (79%) favor ACTs for adults and children, whereas other clinicians seem to favor the ACQ.

Both the ACT and ACQ have decent literature to support their use, he noted. "I use the ACT, but personally, I don't think it makes a difference which you use. I do think it's important to get an objective score for their subjective symptoms to facilitate tracking over time, and to ensure that clinicians are speaking the same language. For example, if someone else sees my patient for some reason, one look at the ACT score will summarize their disease control, as opposed to them having to pull it out of a running narrative history," said Holley.

ACTs are also favored by 39% of NP/PA/RNs, 34% of pediatricians, 27% of PCPs, 16% of critical care medicine physicians, and just 6% of EM physicians. About one third of EM physicians and PCPs (34% each) favor the ACQ, as do 30% of NP/PA/RNs, 29% of pediatricians, 20% of pulmonologists, 17% of allergists/immunologists, and 8% of EM physicians.

Thirty-six percent of all clinicians said they don't use any assessment tool to gauge asthma control in patients with moderate to severe asthma, including 86% of EM physicians and 42% of PCPs – the specialties most apt to report no use.

As for guideline use, 83% of allergists/immunologists and 81% of pediatricians surveyed use the National Asthma Education and Prevention Program (NAEPP) guidelines. Pulmonologists tend to use these guidelines less often (37%), as they also rely on the Global Initiative for Asthma (GINA) (54%) and European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (43%).

About two thirds (62%) of NP/PA/RNs favor the NAEPP guidelines, as do 49% of PCPs and critical care medicine physicians and 31% of EM physicians. Sixty percent of EM physicians don't use guidelines at all.

*Clinicians tend to see a lack of appropriate treatment as the greatest barrier for patients with moderate to severe asthma; 63% of pulmonologists feel this way, as do 60% of allergists/immunologists, 52% of PCPs, 50% of pediatricians, and 45% of NP/PA/RNs, compared with just 32% of EM and critical care medicine physicians.*

## Chief culprits behind poor asthma control

Clinicians tend to see a lack of appropriate treatment as the greatest barrier for patients with moderate to severe asthma; 63% of pulmonologists feel this way, as do 60% of allergists/immunologists, 52% of PCPs, 50% of pediatricians, and 45% of NP/PA/RNs, compared with just 32% of EM and critical care medicine physicians. EM (67%) and critical care medicine (54%) physicians are also more apt to think that the patient not seeing a provider is the greatest barrier.

Overall, most clinicians surveyed link poor asthma control to poor medication adherence and social or environmental risk irritants, such as smoking, secondhand smoke exposure, vaping, and pollutants.

*'We know from data that poor control is related to socioeconomic status and behavioral health.'*

**Dr. Holley**

"No surprise here," said Holley. "In my experience, medication adherence and environmental risks or irritants are big factors in patients with moderate to severe asthma who don't respond to conventional, standard asthma treatment and continue to progress."

"We know from data that poor control is related to socioeconomic status and behavioral health. We also know that proper inhaler use and compliance are a big problem. Does this account for most 'progression'? That's hard to say, I suppose, but certainly these are big factors," Holley added.

Echoing Holley, Navitha Ramesh, MD, clinical assistant professor of medicine at the Department of Clinical Sciences, Geisinger Commonwealth School of Medicine, Scranton, Pennsylvania, who is also a member of the Moderate to Severe Asthma Center of Excellence steering committee, said the biggest barriers to treatment, in her experience, are "poor health literacy, medication nonadherence, poor social support, and tobacco use."

The survey was conducted August 29, 2018, to October 11, 2018. Pulmonologists were recruited from CHEST, and all other clinicians were recruited from Medscape members. Patients with moderate to severe asthma account for at least half of all patients with asthma seen by pulmonologists, allergists/immunologists, and critical care medicine physicians; this proportion falls to about 30% among pediatricians and PCPs. Of the clinicians surveyed, patients with moderate to severe asthma are overwhelmingly referred to pulmonologists. Among the reasons for referral are multiple emergency department visits, poor control, failure on first-line therapy, and confounding factors.

Follow Medscape on Facebook, Twitter, Instagram, and YouTube.

# Envisioning the future: The CHEST Environmental Scan


As a leader in education for pulmonary, critical care, and sleep medicine, staying ahead of trends in its professional fields and across educational delivery, in general, is critical to remaining relevant and to best serve the membership. The leadership of the American College of Chest Physicians (CHEST) developed a multifaceted program this year entitled, "CHEST Inspiration," a series of programmatic initiatives aimed at stimulating and encouraging innovation within the association and recognizing individuals with great ideas that streamline current processes or disrupt ways of traditional thinking about everyday problems.

CHEST® INSPIRATION: Pacing the Future

The CHEST Board of Regents recently completed one of the first components of the CHEST Inspiration program – the 2019 CHEST Environmental Scan. This article describes the development of the 2019 CHEST Environmental Scan and its fit with the other components of CHEST Inspiration program.

Environmental scanning is a formal process for tracking trends and occurrences in an organization's internal and external environment that bear on its success--currently and in the future. The environmental scanning process examines both quantitative and qualitative factors and identifies a set of key environmental indicators believed to have the most important impact on the organization's work.

The 2019 CHEST Environmental Scan is a synthesis of work that took place in January 2019 at the CHEST Environmental Summit, a special joint session of the Board of Regents (BOR) and the CHEST Foundation Board of Trustees (BOT). In that session attendees attempted to free themselves from the usual concentrated focus on the College and Foundation missions, goals, and strategies, recognizing that a possible (even likely) unintended consequence of a narrow focus is losing sight of the outside world and the forces there that—like it or not—influence and could even disrupt the programs and strategies of CHEST and the CHEST Foundation.

To facilitate the process, CHEST engaged a market research and consulting agency with expertise in environmental scans and a client base of nonprofit organizations and associations. The consultant conducted secondary research organized around six drivers of change selected by CHEST leadership:

- Health Care
- Economy and Workforce
- Technology
- Education, Content Delivery, and Career Advancement
- Social, Political, Regulatory, and the Environment
- Philanthropy

The leadership had the opportunity to review the consultant's research findings prior to the Environmental Summit. Then, in the in-person BOT/BOR summit meeting, the consultant's research findings were discussed and debated and were addressed with the following questions:

- How will this trend impact members? How will it change their work environment and what they need to know?
- How will this trend impact CHEST? What are the challenges and opportunities?
- What responses or actions should CHEST take?
- Does this insight require changes to our strategic plan?

The consultant synthesized the debates and discussions and prepared a draft document that shaped this year's document.

The 2019 CHEST Environmental Scan, which will be updated periodically, will be used to:

- Inform members about external developments and put each in perspective
- Help leadership and staff determine future directions and program opportunities
- Keep the 5-year strategic plan fresh and relevant

The environmental scan will be explored in six monthly installments in *CHEST Physician*, with each installment addressing one of the drivers of change. Most of the content is confirming rather than revolutionary in nature. Each installment will be accompanied by comments from one of four leading physician experts who will put the content into perspective.

The two other components of the CHEST Inspiration program are to engage a group of experts from outside the field of medicine and health care who are innovative and successful in their own professions. This focus group of professionals from outside of our association will be held in conjunction with the June Board of Regents meeting. An additional component to stimulate innovative thinking and celebrate great ideas will be a new competitive event at the annual meeting. Dubbed "CHEST FISH BOWL (Furthering Innovation and Science for Health)," this event will launch this month, with contestants submitting video applications that feature their great idea, and winners in select categories will be selected at CHEST 2019 in New Orleans. *CHEST Physician* will be your source for information about all the CHEST Inspiration programs through a new series of articles called "CHEST Inspiration: Pacing the Future."

# Are you up for the challenge? Dr. Salim Surani is!

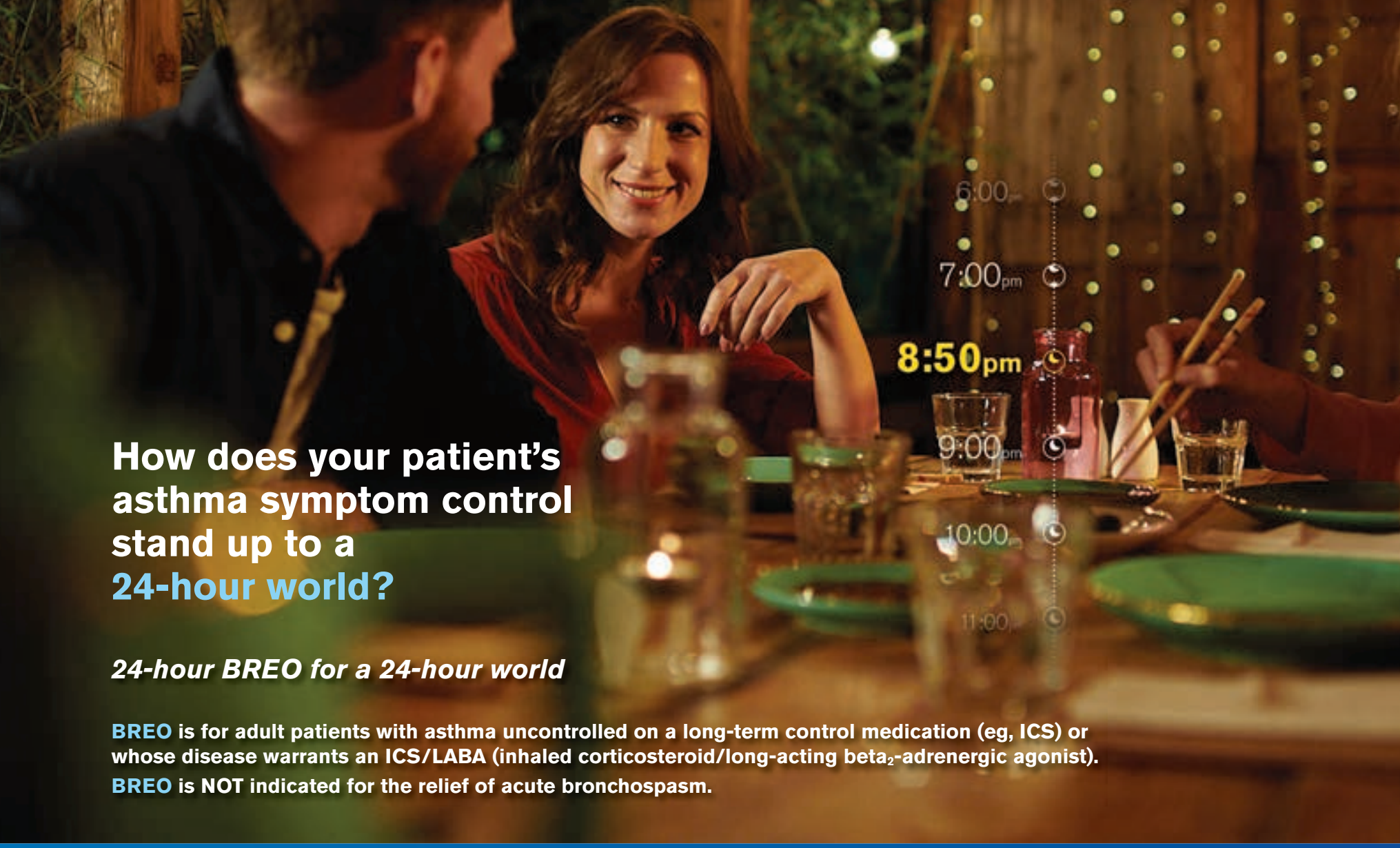
Recently, the CHEST Foundation had the pleasure of sitting down with Salim Surani, MD, FCCP, to get his perspective on the NetWorks Challenge and its impact. Dr. Surani initially got involved with CHEST at the Board level and is now a leader within the Council of NetWorks. "My hope was that I could work within my NetWork to help them become more involved with CHEST and the CHEST Foundation. Through this involvement, I believe we can help shape changes in chest medicine practice dynamics. In the Practice Operations NetWork, we strive to educate physicians in practice to ensure they are up to date with government regulations and how to navigate changes in a positive way, ultimately with the goal of impacting our patients' lives for the better."

When asked about his involvement with CHEST and the Foundation, he said "It just makes sense to be involved in an institution that is passionate about taking care of patients and clinicians. The CHEST Foundation has given tens of millions of dollars in funding for grants to help shape the future of education, the future of research, and the future of better patient care."


**Dr. Surani**

Dr. Surani has always been a strong advocate for the NetWorks Challenge. "There is nothing that has been more satisfying in my life than the opportunity to give. I have always believed that the biggest winner is the person who gives a gift. When you give something to the right cause, what you get in return is a tremendous amount of satisfaction, and it is that satisfaction which drives you – which gives you a feeling of purpose. I want others to get involved and participate. If you feel passionate about something, put your money where your mouth is. This is why I will be matching any gift of $500 or greater by 10% made to any NetWork during the NetWorks Challenge. This is an opportunity to multiply your donation before it goes to the CHEST Foundation so that grants and other awards can be larger in the coming years. The NetWorks Challenge helps fund our Diversity Travel Grants Program and provides additional travel grants to each participating NetWork." Last year, Dr. Surani gave an additional $2,365.17 through his challenge match. Are you up for the challenge this year?

Visit chestfoundation.org/donate today to help shape the future of our discipline!




# How does your patient's asthma symptom control stand up to a 24-hour world?

***24-hour BREO for a 24-hour world***

**BREO is for adult patients with asthma uncontrolled on a long-term control medication (eg, ICS) or whose disease warrants an ICS/LABA (inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist).**

**BREO is NOT indicated for the relief of acute bronchospasm.**

## Important Safety Information

### 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

- LABA monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

### WARNINGS AND PRECAUTIONS (cont'd)

- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO is not a rescue medication and should not be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.
- BREO should not be used more often or at higher doses than recommended, or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing after inhalation.

**Please see additional Important Safety Information for BREO on the following pages.**

**Please see Brief Summary of Prescribing Information for BREO on the pages following this advertisement.**

gsk | INNOVIVA


BREO ELLIPTA
(fluticasone furoate 100, 200 mcg and vilanterol 25 mcg inhalation powder)

# BREO—Lasting efficacy* for a full 24 hours without a second daily dose

In patients uncontrolled on an ICS, in addition to 24-hour lung function improvement,* BREO has been proven to provide:

## Lasting 24-hour asthma symptom control† without a second daily dose


**Lung Function Data**

*In a RDB study of 1039 patients‡ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108-mL improvement from baseline in wm $FEV_1$ (0-24 hours) at the end of the 12-week treatment period vs FF 100 mcg once daily (n=288) (*P*<0.001).[1] In an RDB, placebo-controlled study of 609 patients‡ 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 $FEV_1$ (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).[2]

**Symptom Data**

†In a 12-week, RDB study of 1039 patients‡ symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=345) provided significant 12.2% and 7.8% improvements in the percentages of rescue-free and symptom-free 24-hour periods compared with FF 100 mcg once daily (n=346)(*P*<0.001 and *P*=0.002, respectively).[1]

**BREO is NOT indicated for the relief of acute bronchospasm.**

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

CI=confidence interval; $FEV_1$=forced expiratory volume in 1 second; FF=fluticasone furoate; ICS=inhaled corticosteroid; RDB=randomized, double-blind; wm=weighted mean.

## Important Safety Information (cont'd)

**WARNINGS AND PRECAUTIONS (cont'd)**

- Use caution in patients who use corticosteroids as they 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.
- Particular care is needed for patients transferred from systemic corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREO.
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.
- Caution should be exercised when considering the coadministration of BREO with ketoconazole and other known strong CYP3A4 inhibitors (eg, 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.

**WARNINGS AND PRECAUTIONS (cont'd)**

- Decreases in bone mineral density 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 (eg, 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. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREO long term.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Increased blood glucose levels have been reported. Also, be alert to hypokalemia.
- Orally inhaled corticosteroids may reduce growth velocity in children and adolescents.

**ADVERSE REACTIONS**

- In a 12-week trial, adverse reactions (≥2% incidence and more common than placebo) reported in subjects taking BREO 100/25 (and placebo) were: nasopharyngitis,10% (7%); headache, 5% (4%); oropharyngeal pain, 2% (1%); oral candidiasis, 2% (0%); and dysphonia, 2% (0%). In a separate 12-week trial, adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 (or BREO 100/25) were: headache, 8% (8%); nasopharyngitis, 7% (6%); influenza, 3% (3%); upper respiratory tract infection, 2% (2%); oropharyngeal pain, 2% (2%); sinusitis, 2% (1%); bronchitis, 2% (<1%); and cough, 1% (2%).

**Please see additional Important Safety Information for BREO on all pages.**

**Please see Brief Summary of Prescribing Information for BREO on the pages following this advertisement.**

# BREO has better formulary coverage nationally than Symbicort

Individual access may vary by geography and plan benefit design.
Source: Managed Markets Insight & Technology, LLC, database as of January 2019.


## More Unrestricted Commercial Lives Than Symbicort

## More Unrestricted Medicare Part D Lives Than Symbicort

Nationally, BREO unrestricted commercial lives covered 167.0 million, Symbicort unrestricted commercial lives covered 161.3 million, Medicare Part D BREO unrestricted lives covered 39.4 million, Symbicort unrestricted lives covered 37.0 million.

"Unrestricted coverage" means reimbursement from a health plan without accompanying step edits or prior authorizations.
Commercial lives calculation does not include patient lives associated with Indian Health Services or Department of Veterans Affairs.

"Patient lives" refers to enrollees of a plan, set of plans, or plan segment within a specific area and who may or may not be treated with the product, but have access to the product if it is prescribed. (Source: MMIT).

**What you need to know about this formulary information:**
Formulary status may vary and is subject to change. Formulary comparisons do not imply comparable indications, safety, or efficacy. This is not a guarantee of partial or full coverage or payment. Consumers may be responsible for varying out-of-pocket costs based on an individual's plan and its benefit design. Each plan administrator determines actual benefits and out-of-pocket costs per its plan's policies. Verify coverage with plan sponsor or Centers for Medicare & Medicaid Services. Medicare Part D patients may obtain coverage for products not otherwise covered via the medical necessity process.

## 100% OF ELIGIBLE COMMERCIALLY INSURED PATIENTS CAN GET BREO[§||]


A coupon for eligible patients to pay no more than $10 for each prescription (or per 30-day supply) for up to the first 12 months.

[§]Offer is good for up to 12 uses. Patients in government programs, including Medicare, are not eligible for savings offers. Patients 65 and older will be considered Medicareeligible. Please see the savings offer for complete rules and eligibility.

[||]Eligible patients without insurance to cover the cost of their prescription will receive up to $100 in savings on each 30-day supply of BREO. Patients will be responsible for any remaining out-of-pocket cost. Please visit GSKforyou.com for more details.

### Discover how at SavingsOfferForBREO.com

## Important Safety Information (cont'd)

### ADVERSE REACTIONS (cont'd)

- Additional adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 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 ≥1 asthma exacerbations in the past year, asthma-related hospitalizations occurred in 1% of subjects taking BREO 100/25. No asthma-related deaths or intubations were observed.

### DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of BREO with ketoconazole and other known strong CYP3A4 inhibitors. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- 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 they may potentiate the effect of vilanterol on the cardiovascular system.

### 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 produce severe bronchospasm in patients with COPD or asthma.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.

### USE IN SPECIFIC POPULATIONS

- BREO is not indicated for children and adolescents; the safety and efficacy in patients aged ≤17 years 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.

**References: 1.** Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma*. 2015;52(10):1073-1083. **2.** Bleecker ER, Lötvall J, O'Bryne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2(5):553-561.

BREO ELLIPTA was developed in collaboration with INNOVIVA




BREO ELLIPTA
(fluticasone furoate and vilanterol inhalation powder)

**BREO ELLIPTA**
**(fluticasone furoate and vilanterol inhalation powder)**
The following is a brief summary only and is focused on the asthma indication; see full prescribing information for complete product information.

## INDICATIONS AND USAGE

**1.2 Treatment of Asthma:** BREO is indicated for the once-daily treatment of asthma in patients aged 18 years and older. BREO should be used for patients not adequately controlled on a long-term asthma control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta$_2$-adrenergic agonist (LABA). 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 chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*, and 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 Serious Asthma-Related Events – Hospitalizations, Intubations, Death:** Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death *[see Salmeterol Multicenter Asthma Research Trial (SMART)]*. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone *(see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists)*. Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists: Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma related. The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone. These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS. In a meta-analysis of serious asthma-related events in subjects with asthma aged 12 years and older taking an ICS/LABA (n=17,537) or ICS (n=17,552), events included: serious asthma-related event (number of subjects with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later; subjects can have one or more events, but only the first event was counted for analysis; a single, blinded, independent adjudication committee determined whether events were asthma related), 116, 105 (hazard ratio [95% CI], estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials: 1.10 [0.85, 1.44]); asthma-related death, 2, 0; asthma-related intubation (endotracheal), 1, 2; asthma-related hospitalization (≥24-hour stay), 115, 105. Subjects on ICS/LABA or ICS were randomized and had taken at least 1 dose of study drug. Planned treatment was used for analysis. The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27). Salmeterol Multicenter Asthma Research Trial (SMART): A 28-week, placebo-controlled, U.S. trial that compared the safety of 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 versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

**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$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of BREO with a higher strength, adding additional ICS, or initiating systemic corticosteroids. Patients should not use more than 1 inhalation once daily of BREO. BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist. When beginning treatment with BREO, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

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

**5.4 Local Effects of Inhaled Corticosteroids:** 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 ($FEV_1$ or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

**5.8 Hypercorticism and Adrenal Suppression:** Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*. Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

**5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:** Caution should be exercised when considering the coadministration of BREO with 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 increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

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

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

**5.12 Cardiovascular Effects:** Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in subjects with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

**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. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREO long term.

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

**5.16 Hyperglycemia and Hypokalemia:** There have been reports of increases in blood glucose levels with BREO. This should be considered in patients with a history of, or with risk factors for, diabetes mellitus *[see Adverse Reactions (6.3)]*. 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. In clinical trials evaluating BREO in subjects with COPD or asthma, there was no evidence of a treatment effect on serum 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

Use of LABA may result in the following: serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1)]* and cardiovascular effects *[see Warnings and Precautions (5.12)]*. 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)]*, and 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 2 long-term trials.

12-Week Trials: Trial 1 was a 12-week trial that evaluated the efficacy of BREO 100/25 in adult and adolescent 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) in subjects with asthma taking BREO 100/25 (n=201), fluticasone furoate 100 mcg (n=205), or placebo (n=203), respectively, were: nasopharyngitis, 10%, 7%, 7%; oral candidiasis (includes oral candidiasis and oropharyngeal candidiasis), 2%, 2%, 0%; headache, 5%, 4%, 4%; oropharyngeal pain, 2%, 2%, 1%; dysphonia, 2%, 1%, 0%. Trial 2 was a 12-week trial that evaluated the efficacy of BREO 100/25, BREO 200/25, and fluticasone furoate 100 mcg in adult and adolescent subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years. In Trial 2, adverse reactions (≥2% incidence) in subjects with asthma taking BREO 200/25 (n=346), BREO 100/25 (n=346), or fluticasone furoate 100 mcg (n=347), respectively, were: headache, 8%, 8%, 9%; nasopharyngitis, 7%, 6%, 7%; influenza, 3%, 3%, 1%; upper respiratory tract infection, 2%, 2%, 3%; sinusitis, 2%, 1%, <1%; bronchitis, 2%, <1%, 2%; oropharyngeal pain, 2%, 2%, 1%; 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 adult and adolescent 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 noted for Trials 1 and 2, adverse reactions occurring in ≥2% of subjects treated with BREO 200/25 included viral respiratory tract

*(continued on next page)*

*(continued from preceding page)*

infection, pharyngitis, pyrexia, and arthralgia. 12-Month Trial: Long-term safety data are 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 adult and adolescent 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 noted for Trials 1 and 2, adverse reactions occurring in ≥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 1 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. Metabolism and Nutrition Disorders: hyperglycemia. Musculoskeletal and Connective Tissue Disorders: muscle spasms. Nervous System Disorders: tremor. Psychiatric Disorders: nervousness. Respiratory, Thoracic, and Mediastinal Disorders: paradoxical bronchospasm.

## 7 DRUG INTERACTIONS

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy:** Risk Summary: There are insufficient data on the use of BREO, fluticasone furoate, or vilanterol in pregnant women. There are clinical considerations with use of BREO in pregnant women. *(See Clinical Considerations.)* In an animal reproduction study, fluticasone furoate and vilanterol administered by inhalation alone or in combination to pregnant rats during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate and vilanterol doses in this study were approximately 5 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 200 and 25 mcg in adults, respectively. *(See Data.)* The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations: *Disease-Associated Maternal and/or Embryofetal Risk:* In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control of asthma. *Labor and Delivery:* There are no human studies evaluating the effects of BREO during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of BREO during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. Data: *Animal Data: Fluticasone Furoate and Vilanterol:* In an embryofetal developmental study, pregnant rats received fluticasone furoate and vilanterol during the period of organogenesis at doses up to approximately 5 and 40 times the MRHDID, respectively, alone or in combination (on a mcg/m$^2$ basis at inhalation doses up to approximately 95 mcg/kg/day). No evidence of structural abnormalities was observed. *Fluticasone Furoate:* In 2 separate embryofetal developmental studies, pregnant rats and rabbits received fluticasone furoate during the period of organogenesis at doses up to approximately 4 and 1 times the MRHDID, respectively (on a mcg/m$^2$ basis at maternal inhalation doses up to 91 and 8 mcg/kg/day). No evidence of structural abnormalities in fetuses was observed in either species. In a perinatal and postnatal developmental study in rats, dams received fluticasone furoate during late gestation and lactation periods at doses up to approximately 1 time the MRHDID (on a mcg/m$^2$ basis at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed. *Vilanterol:* In 2 separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 1,000 times, respectively, the MRHDID (on a mcg/m$^2$ basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 160 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID (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. In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m$^2$ basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

**8.2 Lactation:** Risk Summary: There is no information available on the presence of fluticasone furoate or vilanterol in human milk, the effects on the breastfed child, or the effects on milk production. Low concentrations of other ICS have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BREO and any potential adverse effects on the breastfed child from fluticasone furoate or vilanterol or from the underlying maternal condition.

**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 1 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) of full Use in Special Populations (8.4) of full prescribing information]*.

**8.5 Geriatric Use:** Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO for COPD included 4,820 subjects aged 65 and older and 1,118 subjects aged 75 and older. Clinical trials of BREO for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

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

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

## 10 OVERDOSAGE

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

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

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

## 17 PATIENT COUNSELING INFORMATION

*See FDA-Approved Patient Labeling*

Serious Asthma-Related Events: Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used together, such as with BREO, there is not a significant increase in the risk of these events. 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, treat it 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. Glaucoma and Cataracts: Advise patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations. Risks Associated with Beta-agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Hypersensitivity Reactions, Including Anaphylaxis: Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.



Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709


FFVJRNA190001 March 2019
Produced in USA.

PULMONARY PERSPECTIVES®

# Endobronchial valves for lung volume reduction: What can we offer patients with advanced emphysema?

BY CATHERINE L. OBERG, MD; JASON A. BEATTIE, MD; AND ERIK E. FOLCH, MD, MSC

The global burden of COPD is considerable. In the United States, it is the third most common cause of death and is associated with over $50 billion in annual direct and indirect health-care expenditures (Guarascio AJ, et al. *Clinicoecon Outcomes Res.* 2013;5:235). For patients with severe emphysema with hyperinflation, dyspnea is often a quality of life (QOL)-limiting symptom (O'Donnell DE, et al. *Ann Am Thorac Soc.* 2017;14:S30). Few proven palliation options exist, particularly for patients with dyspnea refractory to smoking cessation, medical management with bronchodilators, and pulmonary rehabilitation. The recent Food and Drug Administration (FDA) approval of two endobronchial valves for lung volume reduction has established the increasing importance of bronchoscopy as a management tool in advanced COPD.

## Why were these valves developed?

For decades, lung volume reduction has been investigated as a mechanical approach to counteract the physiologic effects of emphysematous hyperinflation. Its goal is to improve lung elastic recoil, respiratory muscle mechanical advantage and efficiency, and ventilation/perfusion matching. The landmark National Emphysema Treatment Trial (NETT), published in 2001 and 2003, demonstrated that in a select patient population (upper lobe-predominant emphysema and low exercise capacity), lung volume reduction surgery (LVRS) lowers mortality and improves QOL and exercise tolerance (Fishman A, et al. *N Engl J Med.* 2003;348:2059). Despite the encouraging results in this study subpopulation, LVRS is performed infrequently (Decker MR, et al. *J Thorac Cardiovasc Surg.* 2014;148:2651). Concern about its morbidity and the specialized nature of the procedure has hindered widespread adoption. Subsequently, endobronchial techniques have been developed as an alternative to surgical lung volume reduction.

Dr. Oberg

Dr. Beattie

Dr. Folch

## How does bronchoscopic lung volume reduction (BLVR) benefit patients with emphysema?

Valves used for ELVR are removable one-way flow devices placed by flexible bronchoscopy into select airways supplying emphysematous lung. The valves block air entry but allow the exit of secretions and trapped air. This results in atelectasis of the targeted lobe and a decrease in lung volume.

## Which endobronchial valves are available in the United States?

In 2018, two valves were approved by the FDA for bronchoscopic lung volume reduction (BLVR) – the Zephyr® EBV (Pulmonx) ( (Fig 1) and the Spiration® Valve System (Olympus) (IBV) (Fig 2). The Zephyr® EBV is a duckbill-shaped silicone valve mounted within a self-expanding nitinol (nickel titanium alloy) stent. It comes in three sizes for airways with a diameter 4 - 8.5 mm. The Spiration® IBV umbrella-shaped valve is composed of six nitinol struts surfaced with polyurethane. Its four sizes accommodate airway diameters 5 - 9 mm.

## What's the evidence behind BLVR?

### Zephyr® valves

The Endobronchial Valve for Emphysema Palliation Trial (VENT), the largest valve trial thus far, randomized patients with severe heterogeneous emphysema to receive unilateral Zephyr® valve placement or standard medical care (Sciurba FC, et al. *N Engl J Med.* 2010;363:1233). Overall improvement in spirometry and dyspnea scores was modest in the valve group. Post-hoc analysis identified an important subgroup of patients with significant clinical benefit, those with a complete fissure. This finding gave guidance to further EBV studies on patients with severe emphysema and absent collateral ventilation (CV).

Identifying a complete fissure on imaging is now used as a surrogate for assessing CV and is an integral part of the initial profiling of patients for EBV therapy (Koster TD, et al. *Respiration.* 2016;92[3]:150).

In the STELVIO trial, 68 patients were randomized to Zephyr ® EBV placement or standard medical care (Klooster K, et al. *N Engl J Med.* 2015;373:2325). Those with EBV placement had significantly improved lung function and exercise capacity. TRANSFORM, a multicenter trial evaluating Zephyr® EBV placement in heterogeneous emphysema, showed similar results (Kemp SV, et al. *Am J Respir Crit Care Med.* 2017;196:1535).

The IMPACT trial compared patients with homogenous emphysema without CV to standard medical therapy alone. It showed improve-

*Continued on following page*

# Five traditional New Orleans dishes to try

What makes the traditional New Orleans food so special? The flair and broad history for these dishes unite the city and the love for all things tasty with its seafood, Creole, Cajun, and many other types of food options. We've picked five famous New Orleans dishes that you should try while you attend CHEST 2019.

## Gumbo

As one of Louisiana's quintessential dishes, you can find gumbo in restaurants, at events, and homes all over the state. Claiming both French and West African roots, there's no one way to make gumbo, but it is usually served over rice and with a wide variety of other ingredients. With so many different recipes that each family and cook has perfected to be the "best," most cooks tend to guard their recipes closely.

## Crawfish étoufee

The word étouffée (pronounced eh-too-fey) comes from the French word "to smother." This dish is a very thick stew full of crawfish (or shrimp) served over rice. It is also similar in some way to gumbo – same types of Creole seasonings, served over rice, and made with a roux – but it is often made with a "blonde" roux, which is lighter in color and gives an almost sweet flavor. It's a taste that's worth trying and claimed you won't forget.

## Jambalaya

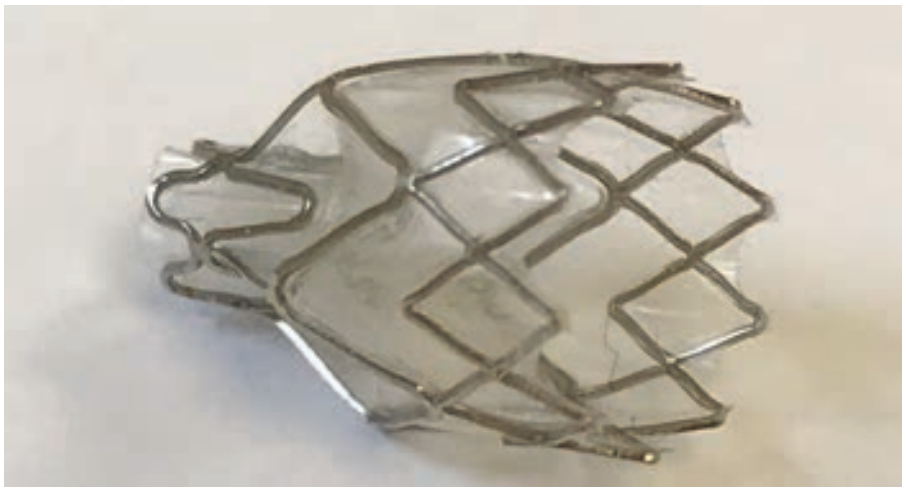
Another famous and traditional New Orleans dish is jambalaya. This is a rice dish that is a culinary staple of the city with a history from the time when colonial Spanish settlers tried reconstructing their native paella from locally sourced ingredients. It typically contains a mix of meat, vegetables, spices, and rice, combined in a variety of ways.

## Po-Boys

This classic French bread sandwich is stuffed and slathered with sauce. Filled with lettuce, tomato, and pickles, it's usually whatever filled with whatever meat you choose – roast beef, fried shrimp, oysters. This allows for many types of po-boy sandwiches. You tend to see very creative po-boys at the Oak Street Po-Boy Festival each year.

## Beignets

These pastries are more than just a doughnut and are famous for being a doughnut without the hole. As the city's most popular sweet treat and staple, locals and visitors can enjoy beignets all year long, available 24-hours a day in New Orleans at more than one coffee hotspot.



Zephyr® valve

Spiration® valve

PHOTOS COURTESY DR. CATHERINE L. OBERG

*Continued from previous page*

ment in $FEV_1$, QOL scores, and exercise tolerance in the EBV group. This study affirmed that the absence of CV, rather than the pattern of emphysema, correlates with the clinical benefit from EBV therapy (Valipour A, et al. *Am J Respir Crit Care Med.* 2016;194[9]:1073). Finally, LIBERATE, a multicenter study on the Zephyr® EBV, examined its placement in patients with heterogenous emphysema. This study demonstrated improvement in spirometry, QOL, and 6-minute walk test (6-MWT) distance (Criner GJ, et al. *Am J Respir Crit Care Med.* 2018;198:1151) over a longer period, 12 months, bolstering the findings of prior studies. These results prompted the Zephyr® valve's FDA approval.

## Spiration® valves

Small trials have shown favorable results with the Spiration® IBV for BLVR, including a pilot multicenter cohort study of 30 patients with heterogeneous, upper-lobe emphysema who underwent valve placement (Wood DE, et al. *J Thorac Cardiovasc Surg.* 2007;133:65). In this trial, investigators found significant improvement in QOL scores, but no change in $FEV_1$ or other physiologic parameters.

The EMPROVE trial is a multicenter, prospective, randomized, controlled study assessing BLVR with the Spiration® IBV. Six- and twelve-month data from the trial were presented in 2018 at the American Thoracic Society Conference and at the European Respiratory Society International Conference.

## Collateral ventilation

Identifying patients in whom there is no CV between lobes is critical to success with BLVR. Collateral ventilation allows air to bypass the valve occlusion distally, thereby negating the desired effect of valve placement, lobar atelectasis. High-resolution computed tomography (HRCT) scanning combined with quantitative software can be used to assess emphysema distribution and fissure integrity. Additionally, a proprietary technology, the Chartis System®, can be employed intra-procedure to estimate CV by measuring airway flow, resistance, and pressure in targeted balloon-occluded segments. Absence of CV based on Chartis evaluation was an inclusion criterion in the aforementioned valve studies.

Which patients with emphysema should be referred for consideration of valve placement?

The following criteria should be used in selecting patients for referral for BLVR:

- $FEV_1$ 15% - 45% of predicted value at baseline
- Evidence of hyperinflation: TLC greater than or equal to 100% and RV greater than or equal to 175%
- Baseline postpulmonary rehabilitation 6-MWT distance of 100 - 500 meters
- Clinically stable on < 20 mg prednisone (or equivalent) daily
- Nonsmoking for at least 4 months
- Integrity of one or both major fissures at least 75%
- Ability to provide informed consent and to tolerate bronchoscopy

## Complications

The most common complication after valve placement is pneumothorax – a double-edged sword in that it typically indicates the achievement of atelectasis. In published trials, the frequency of pneumothorax varies. Some studies document rates below 10%. Others report rates of nearly 30% (Gompelmann D, et al. *Respiration.* 2014;87:485). In landmark trials, death related to pneumothorax occurred rarely. Most severe pneumothoraces occur within the first 72 hours after valve placement. This has prompted many centers to observe postprocedure patients in hospital for an extended period. Pneumonia and COPD exacerbations have also been reported after EBV placement. Therefore, in some trials, patients received prophylactic prednisolone and azithromycin. Other less common complications are hemoptysis, granulation tissue formation, and valve migration.

## What's ahead for ELVR?

Overall, valve technology for BLVR is an exciting option in the management of patients with severe emphysema and is now a staple for any advanced emphysema program. Key areas of future interest include management of patients with partial fissures, minimizing adverse procedural effects, and developing programs to optimize and streamline a multidisciplinary approach to timely and efficient referral, assessment, and intervention. As more patients with COPD undergo ELVR, one goal should be to create multi-institution prospective studies, as well as registries to delineate further the optimal use of endobronchial valves for lung volume reduction.

Zephyr® Endobronchial Valve (Pulmonx)

Spiration® Valve System (Olympus)

CRITICAL CARE COMMENTARY

# Not another burnout article

BY ROOZEHRA KHAN, DO, FCCP

## Does this sound like your day?

You show up to work after a terrible night's sleep. Your back is tense, and you do some kind of walking/stretching combo as you walk through the doors. Your focus fades during the mind-numbing routine of the morning shift sign out. As the day moves forward, you begin to feel resentful as you sign orders, see patients, and address your ICU team needs. You know that's not right, that it's not in line with who you want to be, but the irritation doesn't go away.

Your lunchtime is filled with computer screens, notes, billing, and more billing. The previous feelings of irritation begin to boil into anger because more of your day is filled with bureaucratic demands and insurance reports rather than actually helping people. This isn't what you signed up for. Years and years of training so you could be a paper pusher? The thought leads to rage ... or sometimes apathy on days you give in to the inevitable.

You finish your shift with admissions, procedures, code blues, and an overwhelming and exhausting night shift sign out. You feel like a hamster in a wheel. You're going nowhere. What's the point of all of this? You find yourself questioning why you went into medicine anyways ... yeah, that's burnout.

I know what you're thinking. You keep hearing about this, and it's important to recognize, but then you hear the same old solutions: be more positive, find balance, do some yoga, take this resilience module, be mindful (what on earth does this mean anyways?), get some more sleep. Basically, it's our problem. It's our burden. If all of these were easy to understand and implement, don't you think doctors and healthcare providers would have done it already? I think you and I are a lot alike. These were my exact feelings. But stick with me on this one. I have a solution for you, albeit a little different. I'll show you a more "positive" spin on the DIY.

I burned out early. After fellowship, I didn't want to be a doctor anymore. I desperately sought to alter my career somehow. I looked into website development, something I had been good at in high school. I took a few refresher classes on my days off and started coding my own sites, but I had bills to pay. Big bills. Student loan bills. Luckily, my first job out of fellowship accepted many of my schedule demands, such as day shifts only, and after about a year, I recovered and remembered why I had loved medicine to begin with.

## What is burnout?

Mind-body-soul exhaustion caused by excessive stress. Stress and burnout are closely related, but they're more like distant cousins. Stress can be (and is) a normal part of our jobs. I bet you think you're stressed, when you're probably burned out. Critical care doctors have the highest rate of burnout among all physician subspecialties at >55%, and it is even higher in pediatric critical care. (Sessler C. https://www.mdedge.com/chestphysician/article/160951/society-news/turning-heat-icu-burnout). The main difference between stress and burnout is hope. With stress, you still feel like things can get better and you can get it all under control. Burnout feels hopeless.

Dr. Khan

## What are the three core symptoms of burnout?

- Irritability and impatience with patients (depersonalization)
- Cynicism and difficulty concentrating (emotional exhaustion)
- What's the point of all of this? Nothing I do matters or is appreciated (decreased self-efficacy)

Kupicoo / E+

We can talk about the symptoms of burnout all day, but what does that really look like? It looks like the day we described at the beginning. You know, the day that resonated with you and caused you to keep reading.

## Why should we all be discussing this important topic?

Being burned out not only affects us on a soul level (achingly described above), but, more importantly, this can trickle down to our personal lives, family relationships, and how we care for our patients, with some studies showing that it affects our performance and, gulp, patient outcomes. That's scary (Moss M et al. *Crit Care Med*. 2016;44[7]:1414).

## Causes of burnout

There are many causes of burnout, and several studies have identified risk factors. A lack of control, conflicts with colleagues and leadership, and performing menial tasks can add to the irritation of a workday. This doesn't even include the nature of our actual job as critical care doctors. We care for the sickest and are frequently involved in end-of-life care. Over time, the stress morphs into burnout. Female gender is also an independent risk factor for doctors (Pastores SM, et al. *Crit Care Med*. 2019;47[4]:550).

We've identified it. We've quantified it. But we're not fixing it. In fact, there are only a few studies that have incorporated a needs assessment of doctors, paired with appropriate environmental intervention. A study done with primary care doctors in New York City clinics found that surveying a doctor's "wish list" of interventions can help identify gaps in workflow, such as pairing one medical assistant with each attending (Linzer M, et al. *J Gen Intern Med*. 2015;30[8]:1105).

Without more data like these, we're hamsters in a wheel. Luckily, organizations like CHEST have joined together with others to create the Critical Care Societies Collaborative and have an annual summit to discuss research strategies.

## Solutions

Even millennials are sick of the mindful "chore" list. Yoga pants, yoga mats, crystals, chakras, meditation, and the list goes on and on.

What millennials want are work-life integrations that are easy; work-spaces that invite mindful behavior and daily rituals that excite and relax them. Co-working spaces like WeWork have designated self-care spaces.

Self-care is now essential, not an indulgence. I wasn't sure how to create this space in my ICU, so I started small, with things I could carry with myself. The key is to find small rituals with big meanings. What could this look like for you? I began doing breathwork. Frankly, the idea came to me from my Apple® watch. It just started giving me these reminders one day, and I decided to take it seriously. I found that my mind and muscles eased after only 1 minute of breathing in and out slowly. This elevated my mood and was the refresher I needed in the afternoons. My body ached less after procedures.

I also got a little woo-woo (stay with me now) and began carrying around crystal stones. You don't have to carry around crystals. Prayer books, religious symbols, your child's toy car, anything can work if it has meaning for you, so when you see it or touch it during your day, you remember your big why. Why you're serving people. Why you're a doctor. I prefer the crystals over jewelry because it's something unusual that I don't expect to be sitting in my pocket. It's always a nice gentle reminder of the love I have for my patients, my job, and humanity. When I put my hands in my pocket as I'm talking to yet another frustrated family member, my responses are more patient and more calm, which leads to a more productive conversation.

*Luckily, my first job out of fellowship accepted many of my schedule demands, such as day shifts only, and after about a year, I recovered and remembered why I had loved medicine to begin with.*

Lastly, I started what I call a new Pavlov home routine. When I'm done with work, I light a candle and write out three things I'm grateful for. Retrain your brain. Retrain your triggers. What's your Pavlov's bell going to be? Many of us come home hungry and stressed. Food then becomes linked to stress. This is not good. Link it with something else. Light a candle, count to 3, then blow it out. Use your kids to incorporate something fun. Use a toy with "super powers" to "beam" the bad feelings away. Taking a few extra minutes to shift gears has created a much happier home for me.

There are things that we can't control. That's called circumstances. We can't control other people; we can't control the hospital system; we can't control our past. But the rest of everything we can control: our thoughts, feelings, and daily self-care rituals.

It reminds me of something my dad always said when I was a little girl. When crossing the street, you always look twice, oftentimes thrice. Why be so careful? It's the pedestrian's right of way after all. "Well.." he replied, "If a car hits you, nothing much happens to them, but your entire life will be destroyed, forever."

Stop walking into traffic thinking everything will be okay. Take control of what you can.

Look, I get it. As health-care providers, we are an independent group. But just because you can do it alone, doesn't mean you have to.

Choose one thing. Whether it be something I mentioned or something that came to your mind as you read this. Then, drop me a line at my personal email at roozehra.khan.do@gmail.com. I will send you a reply to let you know I hear you and I'm in your corner.

Burnout happens.

But, so does joy, job satisfaction, and balance. Those things just take more effort.

*Dr. Khan is Assistant Editor, Web and Multimedia, CHEST® journal.*

# CLASSIFIEDS

Also available at MedJobNetwork.com

## PROFESSIONAL OPPORTUNITIES

CHEST NETWORKS

# Pulmonary medicine. Cardiovascular medicine and surgery. Chest infections. Interprofessional team.

## Clinical Pulmonary Medicine

### Pulmonary embolism in pregnancy: A diagnostic conundrum

Pulmonary embolism (PE) is the 6th leading cause of maternal mortality in the United States. The clinical signs and symptoms of PE are usually nonspecific and often overlap with the normal physiologic changes of pregnancy. Due to low specificity and sensitivity of D-dimer test, pregnant patients with suspected PE often undergo CT pulmonary angiography (CTPA) and ventilation-perfusion scanning, both of which can cause radiation exposure to mother and fetus. To answer whether pregnancy-adapted YEARS algorithm (Van der Hulle T et al. *Lancet.* 2017;390[10091]:289) can be safely used to avoid diagnostic imaging, Artemis Study Investigators prospectively studied three criteria from YEARS algorithm in combination with a D-dimer level (Van der Pol et al. *N Engl J Med.* 2019;380[12]:1139). The three criteria included clinical signs of deep-vein thrombosis (DVT), hemoptysis, and PE as the most likely diagnosis. PE was considered ruled out when none of the three criteria were present and D-dimer was less than 1000 ng/mL or if one or more of the criteria were met and D-dimer was less than 500 ng/mL. Patients in whom D-dimer was greater than 1000 ng/mL or in those with D-dimer greater than 500 ng/mL and had one or more of the YEARS algorithm criteria present, PE could not be ruled out and underwent CTPA. A modification of the criteria was done only for patients who had clinical signs of DVT at baseline. These patients underwent compression ultrasonography and, if a clot was found, CTPA was not performed, and patients were started on anticoagulation therapy. Those with negative DVT studies were subclassified based on D-dimer levels as the study population above. Patients in whom pulmonary embolism was not ruled out underwent CTPA. Of these 299 patients, 16 (5.4%) were confirmed to have PE at baseline. In the remaining 195 patients in whom PE was ruled out on the basis of study protocol, a 3-month follow-up diagnosed one patient (0.51%) with VTE. Using pregnancy-adapted YEARS algorithm, CTPA was avoided in 39% of the patients, of which 65% were in their first trimester when the radiation exposure can be most harmful to the fetus.

Dr. Adrish

*Due to low specificity and sensitivity of D-dimer test, pregnant patients with suspected PE often undergo CT pulmonary angiography and ventilation-perfusion scanning, both of which can cause radiation exposure to mother and fetus.*

*Muhammad Adrish, MD, FCCP*
*Steering Committee Member*
*Munish Luthra, MD, FCCP*
*Steering Committee Member*

## Cardiovascular Medicine and Surgery

### Physical examination of low cardiac output in the ICU

Rapid evaluation of shock requires identifying signs of tissue hypoperfusion and differentiating between cardiogenic, obstructive, hypovolemic, and vasodilatory etiologies. Cardiac abnormalities may also contribute to mixed shock states in a broad array of critically ill patients. Left ventricular dysfunction in inpatients correlates with physical exam, with a 2.0 positive likelihood ratio and 0.41 negative likelihood ratio (Simel DL, Rennie D, eds. *The Rational Clinical Examination: Evidence-Based Clinical Diagnosis.* 2009). Accurate clinical assessment of cardiac output, however, is a fraught endeavor. In a recently published large series of patients with unplanned ICU admission, atrial fibrillation, systolic blood pressure (BP) < 90, altered consciousness, capillary refill time > 4.5 seconds at the sternum, or skin mottling over the knee predicted low cardiac output with specificity >90%. Of 280 patients with a cardiac index of < 2.2 L/min/m$^2$, less than half had any one of these findings (Hiemstra, et al. *Intensive Care Med.* 2019;45[2]:190).

Dr. Kenigsberg

Regarding determination of shock etiology, in a small series of patients with systolic blood pressure < 90 mm Hg, physical exam findings of relatively warm skin temperature and rapid capillary refill had 89% sensitivity for vasodilatory shock, and jugular venous pressure ≥8 had 82% sensitivity for cardiogenic etiologies (Vazquez, et al. *J Hosp Med.* 2010;5[8]:471). Thus, while physical exam findings may inform bedside shock assessment, their accuracy is limited. Critical care physicians should consider additional assessment techniques, such as echocardiography or invasive hemodynamic monitoring, if diagnostic uncertainty persists (Vincent, et al. *N Engl J Med.* 2013;369[18]:1726).

*Benjamin Kenigsberg, MD*
*Steering Committee Member*
*Dr. David Bowton and Dr. Steven Hollenberg contributed to the article.*

## Chest Infections

### Lung infections in transplant recipients

The increase in lung transplantation over the years led to lung transplant recipients presenting to pulmonologists outside of specialized centers. One of the most common presentations is for infections. Infections account for more than 25% of all posttransplant deaths (Yusen, et al. *J Heart Lung*

*Transplant*. 2014;33[10]:1009.

Multiple factors contribute to this increased infection risk, including donor lung colonization, disruption of local host defenses, constant contact with environmental pathogens, and heavy immunosuppression (Redmund KF, et al. *Proc Am Thorac Soc*. 2009;6[1]:94).

The onset of infectious manifestations, from the time of transplantation, is variable, depending on the organism. Based on the time of onset, infections can be categorized into within the first month posttransplant, 1 to 6 months, and beyond 6 months, posttransplant. During the first month, because of allograft colonization, preexisting infections in the recipient, and surgical- and hospital-acquired nosocomial infections are more common. The first 6 months are where the patients are at the highest risk for opportunistic infections. As the immunosuppression is lowered after 6 months, the causative organisms tend to be more common pathogens (Green M. *Am J Transplant*. 2013;13 [suppl 4]:3-8).

*Multiple factors contribute to this increased infection risk, including donor lung colonization, disruption of local host defenses, constant contact with environmental pathogens, and heavy immunosuppression.*

An early, aggressive, empiric antimicrobial therapy initiation and proactive, invasive diagnostic approach with needed testing to identify the potential pathogen, is imperative in these patients. Early bronchoscopy with bronchoalveolar lavage remains the most sensitive test to identify pathogens. Therapy can then be tailored toward the identified pathogen.


Dr. Alalawi

As part of the Chest Infections NetWork, we would like to raise awareness of lung infections in unique subgroups, such as lung transplant recipients. Treating infections in such patients requires a high index of suspicion in the setting of an atypical presentation.

*Raed Alalawi, MD, FCCP*
*Steering Committee Member*

**Interprofessional Team**

## Extracorporeal membrane oxygenation (ECMO) in near fatal asthma

Near fatal asthma (NFA) is defined as acute severe asthma characterized by acute respiratory failure with hypercapnia and/or respiratory acidosis requiring ventilator support. NFA refractory to conventional medical management and ventilator therapy can lead to fatal outcomes. Near fatal asthma also carries substantial mortality if invasive ventilation is needed (Marquette CH, et al. *Am Rev Respir Dis*. 1992;146[1]:76). Use of sedatives can exacerbate bronchospasm, and positive pressure ventilation can exacerbate dynamic hyperinflation, impairing hemodynamics, and gas exchange, and leading to barotrauma. This approach seems contrary to the goals of management. Outside of conventional therapies, such as IV steroids and inhaled beta-agonists, the data supporting other therapies such as IV beta-agonists, MgSO4, methylxanthines, mucolytics, heliox, and volatile anesthetics are scant. In contrast, venovenous ECMO can provide adequate gas exchange and prevent lung injury induced by mechanical ventilation and may be an effective bridging strategy to avoid aggressive ventilation in refractory NFA (Hye Ju Yeo, et al. *Critical Care*. 2017;21[1]:297).


Dr. Baeten


Dr. Luthra

Use of early ECMO to permit spontaneous breathing while the circuit accomplishes required ventilation and oxygenation seems more ideal. Avoidance of mechanical ventilation not only prevents complications like barotrauma but also may reduce delirium, malnutrition, and neuromuscular dysfunction. Performing "awake" ECMO has successfully been described for obstructive airway disease (Langer T, et al. *Critical Care*. 2016;20[1]:150). Factors limiting this approach are the invasive nature of ECMO and the inherent risks of large cannula dislodgement; however, the safety of this has been demonstrated with ambulation of ECMO patients to receive physical therapy (Abrams D, et al. *Ann Cardiothorac Surg*. 2019;8[1]:44). Alternatively, extracorporeal carbon dioxide removal (ECCO2R) systems utilize smaller catheters to satisfactorily remove $CO_2$ while oxygen supplementation could be achieved via nasal cannula (Pisani L, et al. *Respiratory Care*. 2018;63[9]:1174). Incorporation of ECMO in select cases of NFA, especially ECCO2R, should be considered as an early rather than rescue therapy for acute severe asthma refractory to conventional medical therapy.

*Performing "awake" ECMO has successfully been described for obstructive airway disease. Factors limiting this approach are the invasive nature of ECMO and the inherent risks of large cannula dislodgement; however, the safety of this has been demonstrated with ambulation of ECMO patients to receive physical therapy.*

*Robert Baeten, DMSc, PA-C, FCCP*
*Steering Committee Member*
*Munish Luthra MD, FCCP*
*Steering Committee Member*

# This month in the journal *CHEST*®

## *Editor's Picks*

BY RICHARD S. IRWIN, MD, MASTER FCCP

**COMMENTARY**

**On Being the Editor in Chief of the Journal *CHEST*: 14 Memorable Years.**
*By Dr. Richard S. Irwin*

**ORIGINAL RESEARCH**

**Procalcitonin-Guided Antibiotic Discontinuation and Mortality in Critically Ill Adults: A Systematic Review and Meta-analysis.**
*By Dr. B. J. Pepper, et al.*

**A Novel Algorithm to Analyze Epidemiology and Outcomes of Carbapenem Resistance Among Patients With Hospital-Acquired and Ventilator-Associated Pneumonia: A Retrospective Cohort Study.**
*By Dr. M. D. Zilberberg, et al.*

**Raw Bioelectrical Impedance Analysis Variables Are Independent Predictors of Early All-Cause Mortality in Patients With COPD.**
*By Dr. Francesca de Blasio, et al.*


# INDEX OF ADVERTISERS

# COVERAGE AND ACCESS SHOULDN'T STAND IN THE WAY OF HER TREATMENT

Coverage and accessibility are among the issues that may be of concern to your patients—and to you. But with broad coverage of TRELEGY, you can write with confidence.

**>81%** of Medicare Part D and Commercial patients nationally are now covered without restrictions*

*TRELEGY is covered without restrictions for 81% of commercial and 81% of Medicare Part D. "Covered without restrictions" is defined as reimbursement from a health plan with no accompanying step edits or prior authorizations.

## Scan this code with your smartphone to see the coverage in your area

**or visit AccessTRELEGY.com**

**What you need to know about this information:**

Individual access may vary by geography and plan benefit design.

Formulary status may vary and is subject to change. Formulary coverage does not imply clinical efficacy or safety. This is not a guarantee of partial or full coverage or payment. Consumers may be responsible for varying out-of-pocket costs based on an individual's plan and its benefit design. Each plan administrator determines actual benefits and out-of-pocket costs per its plan's policies.

Verify coverage with plan sponsor or Centers for Medicare & Medicaid Services. Medicare Part D patients may obtain coverage for products not otherwise covered via the medical necessity process. Source: Managed Markets Insight and Technology, LLC. Database as of March 2019.


TRELEGY ELLIPTA
(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)