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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Courtesy UChicago Medicine

Dr. Matthew M. Churpek and a research team looked at the timing of lactate measurements, the timing of the initiation of treatment, and the impact of these two factors on mortality risk among patients with severe sepsis.

Earlier lactate draw benefits patients with severe sepsis

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL CHEST® ▪ For patients identified as having severe sepsis, delays in lactate measurement were associated with delayed treatment and progressive mortality increases, findings of a retrospective study show.

Those patients had a longer time to administration of IV fluids (IVF) and antibiotics, senior author Matthew M. Churpek, MD, of the department of medicine, University of Chicago, and a team of researchers reported in the journal *CHEST®*.

In previous studies, delayed antibiotics in patients with sepsis has been associated with increased mortality, wrote co-author Xuan Han, MD, and coauthors. "Systematic early lactate measurements when a patient presents with sepsis may thus be useful in prompting earlier, potentially life-saving interventions," they noted.

The retrospective study comprised 5,762 adults admitted to the University of Chicago from November 2008 to January 2016. These patients met criteria for severe sepsis, as outlined in the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), a quality measure introduced by the Centers for Medicare & Medicaid Services in 2015. SEP-1 identifies patients who meet two of four systemic inflam-

LACTATE // *continued on page 4*

CT lung cancer screening remains underutilized

BY SUSAN LONDON
MDedge News

Most heavy smokers in the United States who are eligible for low-dose CT screening for lung cancer do not receive it, according to a cross-sectional study reported at the annual meeting of the American Society of Clinical Oncology.

Results of the National Lung Screening Trial reported in 2011 showed a 20% reduction in lung cancer mortality with targeted low-dose CT (LDCT) screening, noted lead study author Danh C. Pham, MD, of the James Graham Brown Cancer Center at the University of Louisville (Ky.).

Since 2013, the U.S. Preventive Services Task Force has recommended this screening for people aged 55-80 years who are current or former heavy smokers, defined as having smoked at least 30 pack-years, he added. "More importantly, in 2015, the Centers for Medicare & Medicaid Services expanded Medicare coverage for LDCT for lung cancer screening," he said.

However, results of the new study showed

LUNG CANCER // *continued on page 7*

INSIDE HIGHLIGHT

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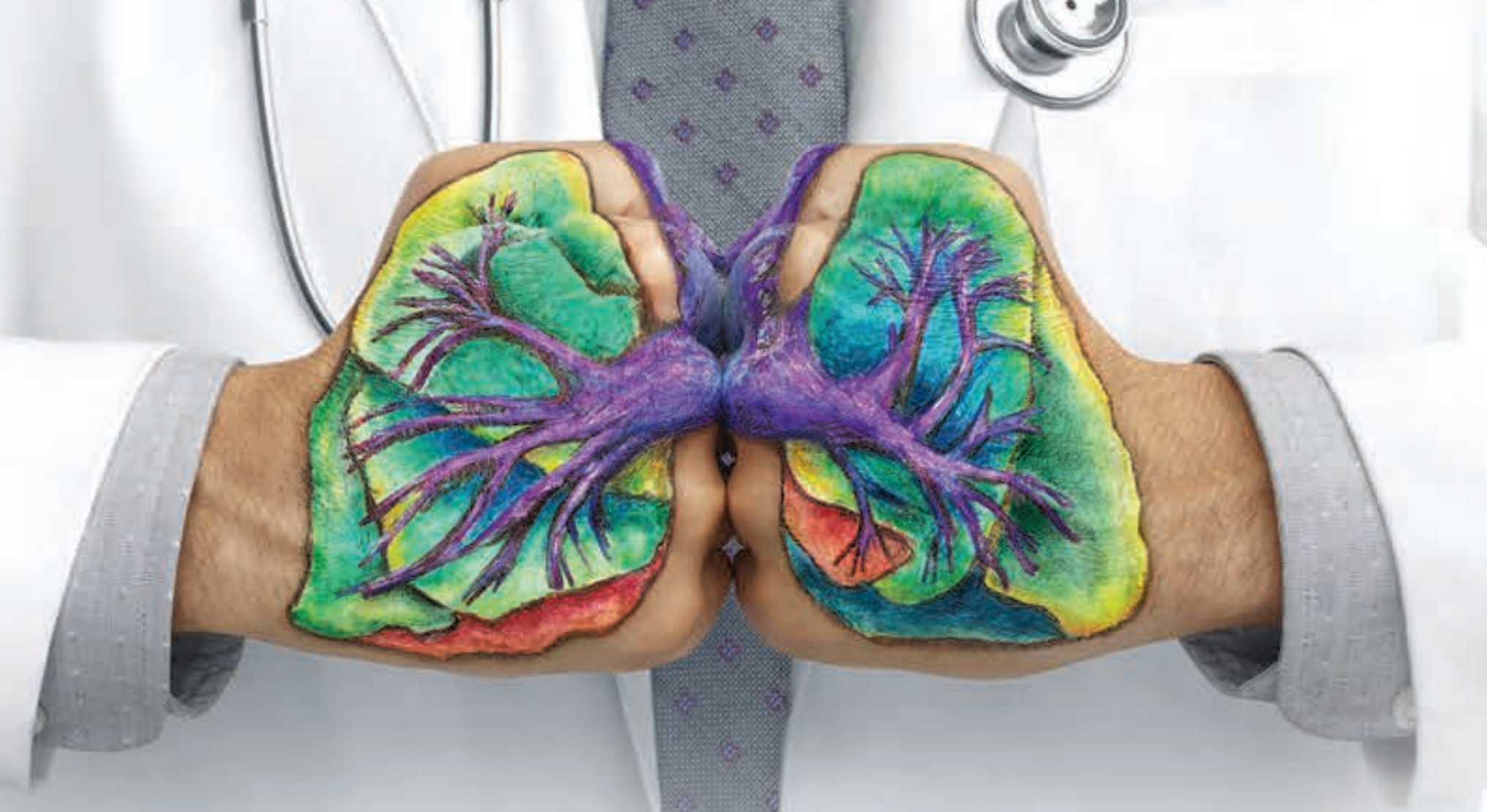

Indication

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

Select Important Safety Information

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

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

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

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

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

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

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

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

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and

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pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.

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

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

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

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

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

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).[2] 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.[3] 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.[4] Esbriet had a significant impact on lung function decline and delayed progression of IPF vs placebo in ASCEND.[2,3] 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).[1,2,4] **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.[2,4]**

†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).[2]

‡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.[2]

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

Delays in lactate measurement led to delays in treatment // continued from page 1

matory response syndrome (SIRS) criteria, display at least one new organ dysfunction, and have documentation of suspicion of infection. Those patients meeting all of these criteria within a 6-hour period are identified as having "severe sepsis." The SEP-1 mandates interventions including lactate draws and antibiotics for patients identified as having severe sepsis via clinical and laboratory evaluation, the authors noted. The investigators assumed that "given prior work suggesting lactate clearance as a goal of sepsis management, it is likely that patients with elevated values would likely receive more aggressive resuscitation."

The Chicago study focused on the timing of lactate measurements, the timing of the initiation of treatment, and the impact of these two factors on mortality risk among these patients.

They found that 60% of these patients identified as having severe sepsis had serum lactate measurements drawn within the time window specified in SEP-1. But timelines varied significantly by setting, at just 32% in patients who first met the criteria on the wards, compared with 55% in the ICU, and

A large number of patients become newly septic on the wards and have higher mortality than those in the ED.

DR. HAN

79% in the emergency department.

In-hospital mortality among the sample was highest in patients with delayed lactate measurements, at 29%, compared with 27% for those with lactates taken within the specified time window, and 23% for sepsis patients who had no lactate draw (*P* less than .01), the researchers reported.

Those patients with higher initial lactate levels and a delay in measurement were at greater risk of death. Among patients with initial lactate levels greater than 2.0 mmol/L was an increased odds of death by 2% for each hour of delay, while no such increase was noted in patients with initial lactates lower than that threshold.

The increased odds of death in patients with higher initial lactates was significant (odds ratio, 1.02; 95% confidence interval, 1.0003-1.05; $P = .04$); however, the association was no longer significant when adjusted for time to IVF and antibiotics ($P = .51$). Based on that observation, the difference in mortality may be due to earlier interventions among patients treated in the specified time frame. Overall, the sooner the lactate measurement was drawn, the sooner treatment was initiated. "Patients with lactates drawn within the SEP-1 window received both IV antibiotics and fluids sooner than their counterparts who had lactates drawn outside of the window," the investigators explained. The timing of treatment initiation reflects the difference between the early and delayed groups: median 2.0 h to receiving antibiotics and 1.3 h to IVF bolus for those whose lactates were measured within the SEP-1 window vs. 3.9 h to antibiotics and 4.8 h to IVF bolus for whose lactate draw was done later, respectively.

Among patients with initial lactate levels greater than 2.0 mmol/L was an increased odds of death by 2% for each hour of delay.

These findings complement prior studies suggesting the benefit of interventions in patients with lactate levels above 2.0 mmol/L, and, conversely, highlight the fact that many patients who meet the severe sepsis criteria nevertheless have normal lactates.

In addition, the investigators noted, "Sepsis bundles have often focused on ED patients, but our study demonstrates that a large number of patients become newly septic on the wards and have higher mortality than those who initially meet criteria in the ED. This is an important population of patients in which to effectively and quickly identify and treat sepsis."

They reported disclosures related to Philips Healthcare, Laerdal Medical, and Quant HC, among other entities.

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SOURCE: Han X et al. Chest. 2018 May 24. doi: 10.1016/j.chest.2018.03.025.

Flu vaccine still not mandatory in many hospitals

BY ANDREW D. BOWSER
MDedge News

Nearly two-thirds of hospitals had mandatory influenza vaccination in place in 2017, up from just one-third in 2013, according to survey responses submitted by infection preventionists working at Veterans Affairs (VA) and non-VA hospitals.

However, that substantial increase was driven almost entirely by the non-VA hospitals: Fewer than 5% of VA hospitals in 2017 had mandatory requirements for health care personnel who provided care for veterans, according to M. Todd Greene, PhD, MPH, with the Patient Safety Enhancement Program at the Veterans Affairs Ann Arbor Healthcare System/University of Michigan and his coauthors.

Despite recommendations to vaccinate health care personnel against influenza, there are several challenges and barriers to implementing the practice, the authors wrote in JAMA Network Open.

JovanMandic/Thinkstock

"Mandating influenza vaccination remains a controversial topic, with uncertainty of the effectiveness of health care personnel influenza vaccination in reducing patient morbidity and mortality, different conclusions regarding the grading of the evidence, and numerous legal and ethical precedents to be carefully considered," they wrote.

Their study was based on 1,062 responses to a panel survey of infection preventionists conducted every 4 years. The survey asked providers about practices used in their hospitals to prevent health care–associated infections.

Compared with 2013, when only 37.1% of non-VA hospitals had mandatory influenza vaccination requirements, the 2017 survey showed a significant increase to 61.4% (P less than .001), Dr. Greene and his colleagues wrote in their report.

By contrast, the proportion of VA hospitals with such requirements increased only slightly, from 1.3% in 2013 to just 4.1% in 2017 (P = .29), the report showed.

Penalties for not complying with the policy were not universal in hospitals with mandates, they added. Only 74% said they had such penalties, and 13% allowed health care personnel to decline influenza vaccination without a specified reason.

After the survey responses were received, the VA issued a directive stating that all health care personnel should receive annual influenza vaccination and should wear masks during influenza season, Dr. Greene noted.

That directive is in line with recommendations from the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices, which have stated that all health care personnel should receive influenza vaccination each year.

In addition, the U.S. Department of Health & Human Services has set a goal of 90% of health care personnel to be vaccinated by 2020, Dr. Green and his coauthors noted.

Mandating influenza vaccination is just one proven successful strategy for increasing coverage at hospitals, according to the study authors. Other approaches include influenza education, incentives, free and easy access to vaccination, and annual campaigns directed at health care personnel, as well as written policies describing the vaccination goal.

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Continued from previous page

"Regardless of whether an organization has an official mandate for vaccinations, establishing a written policy that states the organizational commitment to increasing vaccination rates is among the recommended strategies for improving vaccination coverage among health care personnel," they wrote.

Dr. Greene and his coauthors reported receiving grants from the Blue Cross Blue Shield of Michigan Foundation and the U.S. Department of Veterans Affairs Patient Safety Center of Inquiry during the conduct of the study. One study coauthor reported personal fees from Jvion and from Doximity outside the submitted work.

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SOURCE: Greene MT et al. JAMA Network Open. 2018;1(2):e180143.

VIEW ON THE NEWS

Knowledge gaps remain on vaccination benefit

This study suggests a significant increase in use of mandatory influenza vaccination policies during 2013-2017, driven mainly by increases at non–Veterans Affairs (VA) hospitals and little change at VA facilities. However, there are some caveats to the findings that should be considered, Hilary M. Babcock, MD, MPH, wrote in an editorial referencing the study.

The sample for the 2013 and 2017 surveys included different facilities and different size facilities, so direct comparisons cannot be made, according to Dr. Babcock.

Moreover, the survey questions were worded somewhat differently in the two surveys, and it does not appear that "mandate" was defined by the study authors, she said in her editorial.

The VA recently issued a directive that all health care personnel should receive influenza vaccination and wear masks during influenza season. This new directive provides an "excellent opportunity" to address knowledge gaps regarding the effects of influenza vaccination of health care personnel on patient outcomes, according to Dr. Babcock.

"While the assumption that decreasing the risk of influenza in health care personnel will result in decreased risk of influenza in patients cared for by those health care personnel is common sense, for acute care settings, it is still largely an assumption," Dr. Babcock wrote. "Hopefully, the Veterans Health Administration will combine this initiative with thoughtful, planned, patient outcome assessments to help define the anticipated benefit of these efforts."

Dr. Babcock is with Washington University and the BJC HealthCare Infection Prevention & Epidemiology Consortium, both in St. Louis. These comments are derived from her editorial in JAMA Network Open (2018;1[2]:e180144). Dr. Babcock reported no conflict of interest disclosures related to her editorial.

Stigma smoking may deter patients from lung cancer screening

// *continued from page 1*

that nationally only 1.9% of more than 7.6 million eligible current and former smokers underwent LDCT screening in 2016. By region, the South had one of the lowest rates, despite having the most accredited screening sites and the greatest number of eligible patients.

The findings are stark when juxtaposed with rates of screening for some other cancers, Dr. Pham maintained. For example, 65% of women aged 40 years or older underwent mammography for breast cancer screening in 2015.

"This ultimately begs the question as to the root of the disparity," he said. "Are physicians not referring enough? Or perhaps, are eligible patients not wanting screening, even if they know a test is available? Unfortunately, controversy still exists among providers about costs and benefits of screening, while patients at risk for lung cancer also perhaps lack adequate awareness of the benefits of screening."

It is also possible that the stigma attached to smoking, a modifiable risk factor, and thus to lung cancer screening may be a deterrent, Dr. Pham speculated. Specifically, patients may perceive screening-detected lung cancer as confirmation of a poor lifestyle choice.

"Regardless of the reason, this ultimately is a call to action on everyone's part to increase this much-needed screening, whether that's through creating awareness or conducting additional research, to urgently increase screening for the No. 1 cancer killer in America, as it has been now documented that effective screening can prevent nearly 12,000 premature lung cancer deaths per year," he concluded.

Oncologists in the lung cancer field "would certainly like to be put out of business by an effective screening program," commented ASCO President Bruce E. Johnson, MD, FASCO.

These new findings should be considered in light of the fact that the study period came only about a year after the change in reimbursement for LDCT, he noted. "So this is not a measure of the steady-state situation, but rather when this was first implemented."

Nonetheless, it is "very disappointing" how little LDCT screening is being used, added Dr. Johnson, who is also a professor of medicine at the Dana-Farber Cancer Institute in Boston, and a leader of the center's lung cancer program. "It should be saving 12,000 lives a year, and with this number, it's about 250 lives. As correctly stated, there is a certain stigma whereby people who smoke feel as if they deserve it or that it's sort of a self-punishment."

Policy changes

Policy change would likely help increase uptake of LDCT lung cancer screening, according to Dr. Pham. "I think the most radical thing we could suggest based on our study so far would potentially be making lung cancer screening a national quality health measure, just the way that CMS made [mammograms for] breast cancer and colonoscopies [for colorectal cancer] national areas of improvement in 2008," he elaborated.

"I agree that that could be an effective strategy, particularly since physicians are increasingly being required [to follow] our quality measures to optimize the reimbursement," commented Richard L. Schilsky, MD, FACP, FASCO, chief medical officer of ASCO and press briefing moderator.

DR. PHAM

"Keep in mind that, generally speaking, screening of healthy or high-risk individuals for cancer is typically performed by primary care physicians, not by oncologists," he further noted. "So one of the things that we also need to do is to be sure that primary care physicians are well aware of the screening data and the importance of referring the appropriate patients for screening, and are aware of screening centers available in their communities."

Dr. Johnson said that the society has been active in that area. "ASCO is working with the American College of Physicians and some of the other primary care groups to try to get the message out about the screening," as well as to educate them about the large potential impact of screening and treatment. "There are 15 million cancer survivors in the United States, and for the people who fit those criteria for smoking, [we need] to make certain they are getting screened."

Study details

For the study, Dr. Pham and his colleagues used data from the American College of Radiology's Lung Cancer Screening Registry, collecting total number of LDCTs performed in 2016 from all 1,796 accredited radiographic screening sites. They also used data from the 2015 National Health Interview Survey to estimate eligible smokers who could be screened based on the USPSTF recommendations.

Overall, 1.9% of 7,612,975 eligible current and former heavy smokers underwent LDCT, he reported. By census region, the rate was highest in the Northeast (3.5%) and lowest in the West (1.0%).

Notably, only 1.6% of eligible heavy smokers in the South underwent LDCT, even though that region had, by far, the most accredited screening sites (663) and the most eligible patients (3,072,095). The rate was highest in the Northeast, at 3.5%, even though that region had the second-lowest number of accredited screening sites (404) and the fewest eligible patients (1,152,141).

Dr. Pham disclosed no relevant conflicts of interest. The study received grant funding from the Bristol-Myers Squibb Foundation.

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SOURCE: Pham DC et al. ASCO 2018, Abstract 6504.

Vaccine nonmedical exemptions creating metro 'hotspots' across the United States

BY RICHARD FRANKI
MDedge News

Recent increases in nonmedical exemptions (NMEs) to vaccination have created metropolitan "hotspots" with large numbers of unvaccinated children, according to a report published June 12 in PLoS Medicine.

Since 2009, NMEs based on philosophical beliefs have increased in 12 of the 18 states that currently allow them, although rates seem to have plateaued in some states since 2014. As a result of those increases, there were, during the 2016-2017 school year, 15 metro areas with kindergarten NME populations over 400, reported Jacqueline K. Olive, and her associates at Baylor College of Medicine. Their report was based on data from state health departments and the Centers for Disease Control and Prevention.

Leading the way was Maricopa County, Ariz., home of Phoenix and 2,947 unvaccinated kindergartners, which was more than triple the number in county/city No. 2, Salt Lake County/Salt Lake City (NME total, 956). Close behind in third was King County, Wash. (Seattle), at 940, followed by Multnomah County, Ore. (Portland) at 711 and Oakland County, Mich. (Troy), at 686, the investigators said.

Other hotspots not indicated on the map are: Wayne County, Mich. (Detroit); Allegheny County, Pa. (Pittsburgh); Travis County, Tex. (Austin); Jackson County, Mo. (Kansas City); and Spokane County, Wash. (Spokane).

In addition to the large-population hotspots, there are also a number of mainly rural counties with smaller populations but high NME rates.

Eight of the 10 highest such rates can be found in Idaho, and at the top of that list is Camas County, which had an NME rate of 27% in 2016-2017, the researchers reported.

Analysis of the relationship between NMEs and MMR vaccination showed that "states with more NME students exhibited lower MMR vaccination rates. In contrast, states that have banned NMEs – Mississippi, California, and West Virginia – exhibit the highest MMR vaccine uptake and lowest incidence of vaccine preventable diseases," the investigators wrote.

Ms. Olive and her associates said that there was no specific funding for the study and that no conflicts of interest existed.

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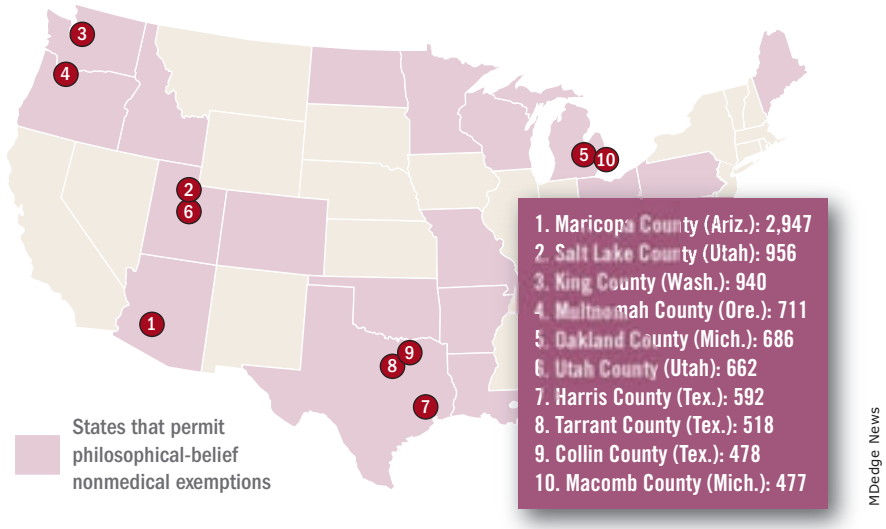
SOURCE: Olive JK et al. PLoS Med. 2018 Jun 12;15(6):e1002578. doi: 10.1371/journal.pmed.1002578.

Metro 'hotspots' with over 400 nonmedical vaccine exemptions



Notes: Based on 2016-2017 data from state health departments and the Centers for Disease Control and Prevention. Data for Texas are from 2015-2016.

Source: PLoS Med. 2018 Jun 12;15(6):e1002578

E-cigarette flavorings foster cardiovascular dysfunction

BY HEIDI SPLETE
MDedge News

Flavorings used in e-cigarettes have a negative impact on endothelial cells that may play a role in cardiovascular toxicity.

Flavored tobacco products are popular among current smokers, including youth, and the flavorings have been deemed ingestible, but their impact on heart health has not been studied, wrote Jennifer Fetterman, PhD, of Boston University, and her colleagues. The report was published in Arteriosclerosis, Thrombosis, and Vascular Biology.

The researchers studied nine types of flavorings used in alternative tobacco products to assess their impact on cardiovascular health.

CARPE89/THINKSTOCK

The first part of the study comprised a population of nine nonsmokers, six nonmenthol cigarette smokers, and six menthol cigarette smokers without cardiovascular disease. The researchers isolated venous endothelial cells from each participant.

Overall, cells from both nonmenthol and menthol cigarette smokers had significantly lower nitric oxide production compared with nonsmokers ($P = .003$ and $P = .012$, respectively). In addition, the flavoring compounds menthol and eugenol impaired nitric oxide production in the cells of healthy individuals.

"Increased inflammation and a loss of nitric oxide are some of the first changes to occur leading up to cardiovascular disease and events like heart attacks and stroke, so they are considered early predictors of heart disease," Dr. Fetterman said in a statement, adding that the "findings suggest that these flavoring additives may have serious health consequences."

To characterize the acute effects of flavoring compounds, the researchers also acquired commercially available endothelial cells and exposed them to nine flavorings: eugenol (clove), vanillin (vanilla), cinnamaldehyde (cinnamon), menthol (mint), 2,5-dimethylpyrazine (strawberry), diacetyl (butter), isoamyl acetate (banana), eucalyptol (mint), and acetylpyridine (burnt).

All nine flavorings induced cell death at the highest concentration tested, ranging from 10 to 100 mmol/L).

The study findings were limited by several factors, primarily a lack of data on how heating the flavorings in the in vitro part of the study might have affected toxicity in the body, the researchers noted.

"Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an e-cigarette," they said.

However, data support the need for regulation and limits on the level of flavorings used in e-cigarettes and other tobacco products, they emphasized.

"These findings suggest that flavoring compounds induce endothelial cell dysfunction in human cells similarly to the abnormal function in active cigarette smokers," the researchers noted.

The study was funded by the National Heart, Lung, and Blood Institute; Food and Drug Administration Center for Tobacco Products; and the American Heart Association. The researchers had no financial conflicts to disclose.

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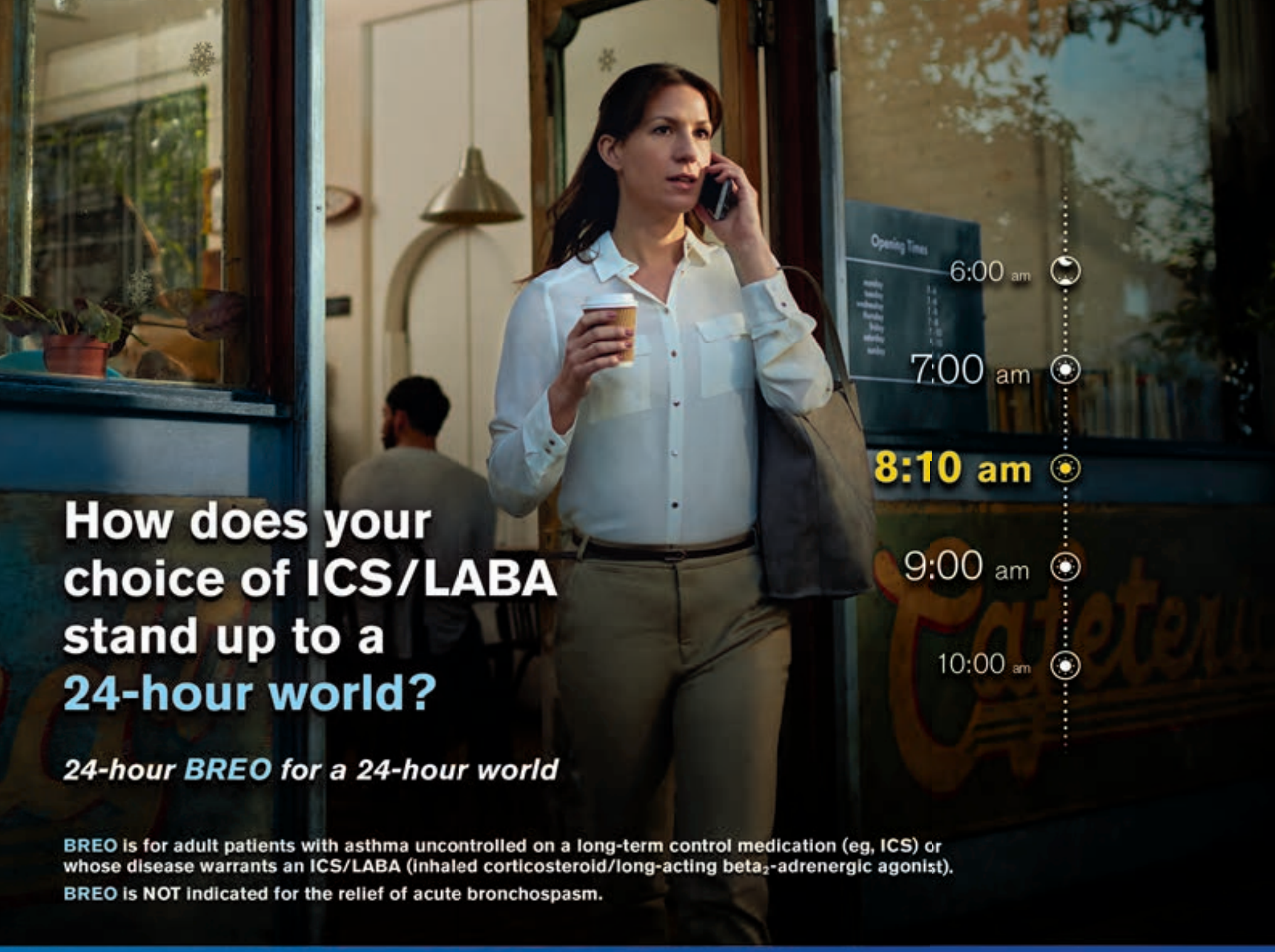
SOURCE: Fetterman J et al. Arterioscler Thromb Vasc Biol. 2018. doi: 10.1161/ATVBAHA.118.311156.



How does your choice of ICS/LABA 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)

24-hour BREO for a 24-hour world

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

PROVIDE 24-HOUR EFFICACY WITH JUST ONE DAILY INHALATION FOR BETTER BREATHING ALL DAY AND NIGHT*

REDUCE EXACERBATIONS IN PATIENTS WITH A HISTORY OF EXACERBATIONS WITH JUST ONE DAILY INHALATION†

*In a randomized, double-blind (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 weighted mean (wm) FEV_1 (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) ($P<0.001$) (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; $P=0.06$]).[1,2]

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

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

FEV_1=forced expiratory volume in 1 second.

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 long-term 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. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.
- Orally inhaled corticosteroids may 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 April 2018.

4 Million
More Unrestricted **Commercial** Lives Than Symbicort

2 Million
More Unrestricted **Medicare Part D** Lives Than Symbicort

"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.

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.

Nationally, BREO Unrestricted Commercial Coverage 164 Million; Symbicort Unrestricted Commercial Coverage 160 Million. Medicare Part D BREO Unrestricted Lives covered 38 Million; Symbicort 36 Million.

100% of eligible commercially insured patients pay no more than $10 a month

A coupon for eligible patients to pay no more than $10 for each prescription for up to 12 months of BREO (30-day supplies). Patients CANNOT use this coupon offer if they are Medicare eligible or government program participants. For coupon eligibility purposes, all those 65 or older will be considered Medicare eligible. Please see the savings offer for complete rules and eligibility.

Discover how at www.24hourworld.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 long-term 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. **3.** Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. *Thorax*. 2014;69(4):312-319.

BREO ELLIPTA was developed in collaboration with INNOVIVA

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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 long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and 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. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

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

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

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

6 ADVERSE REACTIONS

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.

(continued on next page)

6.2 Clinical Trials Experience in Asthma: (cont'd) 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 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. Musculoskeletal and Connective Tissue Disorders: muscle spasms. Nervous System Disorders: tremor. Psychiatric Disorders: nervousness. Respiratory, Thoracic, and Mediastinal Disorders: paradoxical bronchospasm.

7 DRUG INTERACTIONS

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

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

7.3 Beta-adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of BREO, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents 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 inhaled corticosteroids 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); 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. Ocular Effects: Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations. Risks Associated with Beta-agonist Therapy: Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Hypersensitivity Reactions, Including Anaphylaxis: Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Instruct patients to discontinue BREO if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO.

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Hospital-acquired conditions drop 8% since 2014

BY MICHELE G. SULLIVAN
MDedge News

From 2014 to 2016, the rate of potentially deadly hospital-acquired conditions in the United States dropped by 8% – a change that translated into 350,000 fewer such conditions, 8,000 fewer inpatient deaths, and a national savings of almost $3 billion.

The preliminary new baseline rate for hospital-acquired conditions (HACs) is 90 per 1,000 discharges – down from 98 per 1,000 discharges at the end of 2014, according to the Agency for Healthcare Research and Quality's new report, "AHRQ National Scorecard on Hospital-Acquired Conditions – Updated Baseline Rates and Preliminary Results 2014-2016."

The largest improvements occurred in ventilator-associated pneumonias (down 32% from 2014), central line–associated bloodstream infections (down 31%), postoperative venous thromboembolism (21%), and adverse drug events (15%). A new category, *C.difficile* infections, also showed a large decline over 2014 (11%).

These numbers build on earlier successes associated with a national goal set by the Centers for Medicare & Medicaid Services to reduce HACs by 20% by 2019. They should be hailed as proof that attention to prevention strategies can save lives and money, said Seema Verma, CMS administrator.

"Today's results show that this is a tremendous accomplishment by America's hospitals in delivering high-quality, affordable healthcare," Ms. Verma said in a press statement. "CMS is committed to moving the healthcare system to one that improves quality and fosters innovation while reducing administrative burden and lowering costs. This work could not be accomplished without the concerted effort of our many hospital, patient, provider, private, and federal partners – all working together to ensure the best possible care by protecting patients from harm and making care safer."

The numbers continue to go in the right direction, the report noted. Data reported in late 2016 found a 17% decline in HACs from 2010 to 2014. This equated to 2.1 million HACs, 87,000 fewer deaths, and a savings of $19.9 billion.

Much work remains to be done to achieve the stated 2019 goal, the report noted, but the rewards are great. Reaching the 20% reduction goal would secure a total decrease in the HAC rate from 98 to 78 per 1,000 discharges. This would result in 1.78 million fewer HAC in the years 2015-2019. That decrease would ultimately save 53,000 lives and $19.1 billion over 5 years.

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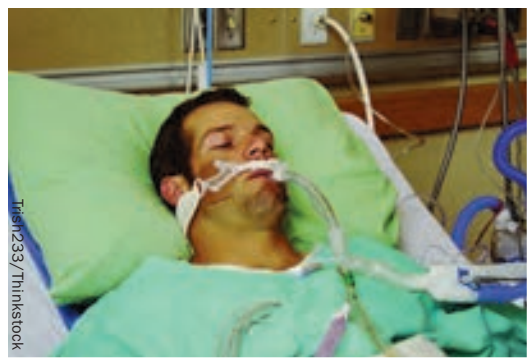

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MDedge News

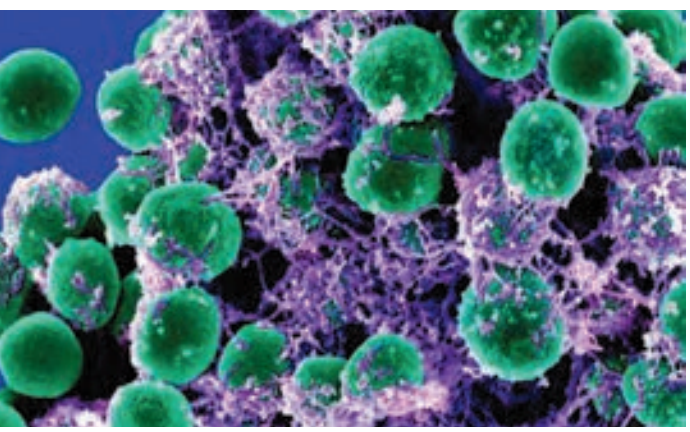
Source: Agency for Healthcare Research and Quality

Systemic changes needed for bronchoscope disinfection

BY JEFF CRAVEN
MDedge News

FROM THE JOURNAL CHEST® ▪ Current guidelines for disinfecting bronchoscopes may not be adequate to prevent transmission of infection, as researchers found all reprocessed bronchoscopes they observed had residual contamination and over half showed microbial growth, according to results from a recent study in *CHEST*.

"Evidence-based, bronchoscope-specific reprocessing and maintenance guidelines are needed, along with quality management programs to ensure that these complex processes are carried out effectively," Cori L. Ofstead, MSPH, president and CEO of Ofstead & Associates, and her colleagues wrote in their study. "Shifting toward using sterilized or single-use bronchoscopes could reduce the risk of infection transmission among vulnerable pulmonary patient populations."



National Institute of Allergy and Infectious Diseases

The researchers inspected 24 reprocessed bronchoscopes used clinically (9 pediatric, 9 therapeutic, 6 endobronchial ultrasound) at three U.S. tertiary care centers in 2017 and compared them with two bronchoscopes that had not been used. Of the bronchoscopes observed, all had residual contamination after manual cleaning and high-level disinfection (HLD). Manually cleaned bronchoscopes had microbial growth in 11 of 20 (55%) samples, while 14 of 24 (58%) of HLD samples contained microbial growth. Upon inspection, the researchers said they discovered "oily residue; dried fluid spots; brown, red, and white residue; scratches; insertion tube buckling; and damaged distal ends," while internal inspections yielded "fluid, discoloration, scratches, filamentous debris, and dented channels."

Ms. Ofstead and colleagues noted that, while the first site exceeded national guidelines, sites B and C contained technicians who did not wear personal protective equipment and the sites did not follow national or manufacturer use guidelines, such as passing bronchoscopes "through a window to a clean room for automated cleaning and HLD with peracetic acid in automated endoscope reprocessor," flushing the bronchoscopes with alcohol, drying them with medical-grade forced air pressure, and storing them in a dedicated clean and dry area. Site A had microbial growth in 20% and 50% of manually cleaned and HLD bronchoscopes, respectively; site B had microbial growth in 100% and 75% of manually cleaned and HLD bronchoscopes, respectively; and site C had microbial growth in 83% and 50% of manually cleaned and HLD bronchoscopes, respectively. Among the microbial species identified were "environmental bacteria and normal flora" such as *Bacillus spp* and *Staphylococcus epidermidis*, molds such as *Lecanicillium lecanii* and *Verticillium dahliae*, and pathogens such as *Stenotrophomonas maltophilia* and *Escherichia coli/Shigella spp*.

"The clinical implications for patients are unknown as the study did not involve assessing patients or reviewing medical records," Ms. Ofstead and her colleagues wrote. "However, the results are worrisome as patients undergoing bronchoscopy are commonly at high risk for infection due to transplant status, critical illness, or immune suppression due to malignancy or chronic disease."

Ms. Ofstead and three authors are employees of Ofstead & Associates, which received research funding and speaking honoraria from 3M, Advanced Sterilization Products (Johnson & Johnson), Ambu, Auris Health, Boston Scientific, Cogentix, ConvergAscent, Healthmark Industries, Invendo Medical, Medivators, Nanosonics, and STERIS. Dr. Ferguson has received fees from NeuWave Medical and PPD, research grants and personal fees from OncoCyte, and research grants from Concordia and PneumRx. Dr. Sonetti reported no relevant financial disclosures.

chestphysiciannews@chestnet.org

SOURCE: Ofstead CL et al. Chest. 2018 May 30. doi: 10.1016/j.chest.2018.04.045.

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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.

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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.

Identifying insomnia in patients with mental disorders

BY BIANCA NOGRADY
MDedge News

The Insomnia Severity Index might be the most effective screening tool at identifying insomnia among outpatients with mental disorders, according to a study published in Sleep Medicine.

The cross-sectional study compared six self-administered sleep measures – the Pittsburgh Sleep Quality Index, Insomnia Severity Index (ISI), Epworth Sleepiness Scale, Flinders Fatigue Scale, Functional Outcomes of Sleep Questionnaire, and Dysfunctional Beliefs and Attitudes About Sleep Scale – in 400 psychiatric outpatients.

Of those, the Insomnia Severity Index was the most accurate way to discriminate between cases of insomnia and noncases according to both the DSM-5 and ICD-10 criteria. In fact, the Insomnia Severity Index was the only scale that was able to discriminate both with good accuracy.

The area under the curve for the ISI was 0.88 for the ICD definition, and 0.82 for the DSM-5 criteria. Researchers found that the best sensitivity and specificity for the ISI was achieved using cutoff scores of less than or equal to 14 for ICD-10 insomnia and less than or equal to 11 for DSM-5 insomnia.

A cutoff of 14 or above for the ISI yielded a sensitivity of 81.3%, specificity of 80.9%, positive predictive value of 66.7%, and negative predictive value of 90.2%.

The Pittsburgh Sleep Quality Index was found to have good accuracy in discriminating between cases and noncases using the ICD-10 criteria, but had only fair accuracy for the DSM-5 criteria. However, it was slightly better than the ISI at detecting insomnia cases, according to the DSM-5 criteria, in people with either bipolar affective or anxiety disorders.

The Flinders Fatigue Scale, Functional Outcomes of Sleep Questionnaire, and Dysfunctional Beliefs and Attitudes About Sleep Scale all showed fair accuracy for the ICD-10 criteria but low accuracy for the DSM-5 criteria, while the Epworth Sleepiness Scale had low accuracy for the ICD-10 criteria and was nondiscriminatory for the DSM-5 criteria.

'Identifying a self-report sleep measure that can detect clinically significant insomnia ... not only provides the clinicians with the ease of administration but also helps them in detecting and treating psychiatric patients whose conditions may be aggravated by the presence of comorbid insomnia.'

The scales were all self-administered, were designed to take 15 minutes or fewer to complete, and were chosen because they covered the six key aspects of sleep, including sleep quality, daytime sleepiness, sleep-related quality of life, and sleep-disruptive cognitions.

The investigators cited one limitation that might limit the generalizability of their findings: Only outpatients with psychiatric disorders were recruited for the study. Nevertheless, the findings have clinical implications, they wrote. "Identifying a self-report sleep measure that can detect clinically significant insomnia ... not only provides the clinicians with the ease of administration but also helps them in detecting and treating psychiatric patients whose conditions may be aggravated by the presence of comorbid insomnia," wrote Lee Seng Esmond Seow, BA, and his colleagues at the Institute of Mental Health in Singapore.

The study was supported by the Singapore Ministry of Health's National Medical Research Council. No conflicts of interest were declared.

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SOURCE: Seow LSE et al. Sleep Med. 2018 Jan;41:86-93.

Impact of marijuana on sleep not well understood

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – Although the national trend of legalization of marijuana for medical and recreational uses has accelerated, physicians should be cautious about prescribing medical marijuana to treat sleep disorders, a sleep specialist told attendees at the annual meeting of the Associated Professional Sleep Societies.

"Increased legalization of medical marijuana may cause reduction in perception of the risk of potential harm," said Ashima Sahni, MD, of Northwestern University, Chicago.

She noted the long-term implications of marijuana use have been documented, including decreased cognition, lack of motivation, and psychotic effects. Marijuana also appears to affect sleep, although most studies were done in the 1970s and showed mixed results, she said.

"Overall the consensus is that the short-term use of medical marijuana causes an increase in slow-wave sleep [SWS], a decrease in sleep onset latency, a decrease in wake after sleep onset [WASO] and a decrease in REM sleep," Dr. Sahni said. But chronic use decreases SWS and results in inconsistencies in REM sleep patterns and sleep fragmentation. These changes lead to a self-perpetuating negative cycle that causes chronic users to progressively increase their intake, furthering sleep disruption, she noted.

Marijuana withdrawal also can cause significant disturbances in sleep patterns, including reduced total sleep time and SWS, increased WASO, increased REM sleep associated with strange dreams, and increased limb movements during sleep, Dr. Sahni said. "The effects can be seen as early as 24 hours after discontinuation and can last as long as 6 weeks," she said. In addition, poor sleep quality prior to a withdrawal attempt has been linked to relapse (Am J Psychiatry. 2004;161:1967-77).

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The use of medical marijuana in the management of sleep disorders is fraught with controversy, Dr. Sahni said. She reviewed studies investigating the use of dronabinol for obstructive sleep apnea (OSA). "This is not medical marijuana," Dr. Sahni said. "It's a synthetic tetrahydrocannabinol [THC] cannabinoid, which acts on the nonselective CB1 and CB2 agonists," she said. THC is the euphoria-inducing compound in marijuana. While the mechanism of action of dronabinol is similar to marijuana, the pharmacokinetics may differ. Dronabinol has been approved by the Food and Drug Administration for cancer-related nausea and appetite stimulation in AIDS patients. She referred to a proof-of-concept study of 17 patients with OSA in which dronabinol reduced the apnea-hypopnea index (AHI) with no degradation of sleep architecture or serious adverse events (Front Psychiatry. 2013 Jan 22;4:1-5). Dr. Sahni also noted a randomized, placebo-controlled trial of 73 patients that reported an average reduction in AHI of 12.9 (Sleep. 2018 Jan 1;41[1] doi: 10.1093/sleep/zsx184). But she pointed out that the American Academy of Sleep Medicine does not recommend medical cannabis or its synthetic extracts for treatment of OSA (J Clin Sleep Med. 2018 Apr 15;14:679-81).

Insomnia, on the other hand, represents the most common use of medical marijuana for sleep. "Studies have shown mixed results because of differences in the ratios of THC to CBD [corticobasal degeneration] in the forms of marijuana examined," she said. "In the short term, subjective sleepiness is reported to be better, but then the self-perpetuating negative cycle initiates with chronic long-term use."

In treatment of nightmares and posttraumatic stress syndrome, Dr. Sahni cited studies that found "good effects" of medical marijuana use (CNS Neurosci Ther. 2009;15:84-8; J Clin Psychopharmacol. 2014 Oct;34:559-64). For REM behavior disorder, medical marijuana was found to be beneficial in four patients with Parkinson disease (J Clin Pharm Ther. 2014 Oct;39:564-6). In poorly treated restless leg syndrome, medical marijuana was reported to be beneficial (Sleep Med. 2017 Aug;36:182-3).

"It should be noted that these were very small studies and therefore more research is needed before we change our medical practices toward various sleep disorders," Dr. Sahni said.

Dr. Sahni and her coauthors reported having no financial relationships to disclose.

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Poor sleep tied to suicidal behaviors in college students

BY GINA L. HENDERSON
MDedge News

Poor sleep is associated with increased suicidal behaviors in college students – even when controlling for depression, a study of 1,700 students shows.

"Findings suggest that some specific sleep components – shorter sleep duration, more frequent bad dreams, feeling too cold while sleeping, and greater sleep medication use – are particularly associated with increased suicidal behaviors in college students," reported Stephen P. Becker, PhD, of the Cincinnati Children's Hospital Center, and his associates.

The researchers recruited students from two universities. Most of the students were female (65%), white (82%), and in their first year of college (63%). The participants' sleep was assessed using the nine-item Pittsburgh Sleep Quality Index (PSQI), their depressive symptoms were assessed using the Depressive Anxiety Stress Scales-21, and their suicidal behavior was assessed using the Suicidal Behaviors Questionnaire-Revised (SBQ-R), which is a four-item, self-report measure.

About two-thirds of the students (64%) were found to have sleep problems (total PSQI score greater than 5), and 24% were found to have suicide risk (total SBQ-R score of at least 7). Of the students who were found to have suicide risk, 83% also had sleep problems.

Using regression analysis, Dr. Becker and his associates found that the odds of being classified with suicide risk were 6.5 times greater for students with depression and 2.7 times greater for those with sleep problems.

"We found that the four-fifths of college students who were classified with suicide risk were also classified with poor sleep (conversely, almost one-third of the participants classified with sleep problems were also classified with suicide risk). Furthermore, poor sleep remained significantly with increased suicide risk after controlling for sex and depression," the investigators wrote.

In addition, the association between depression and suicidal behaviors/risk was reduced when sleep was adjusted for, suggesting that sleep may mediate the link between depression and suicide

The results add to the literature suggesting that sleep would be an "important component to include in screening and intervention efforts to prevent suicidal ideation and attempts on college campuses," the researchers wrote.

Dr. Becker and the other investigators had no conflicts to disclose.

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SOURCE: Becker SP et al. J Psychiatr Res. 2018 Apr;99:123-8.

CBT-I bests acupuncture for treating insomnia

BY SUSAN LONDON
MDedge News

Cancer survivors who have trouble sleeping saw improvements with both cognitive-behavioral therapy designed specifically for insomnia (CBT-I) and acupuncture, according to results from the randomized, controlled CHOICE trial. But the former is more efficacious.

"Insomnia can have deleterious effects on quality of life and function, and occurs in up to 60% of cancer survivors," lead study author Jun J. Mao, MD, chief of integrative medicine service at Memorial Sloan Kettering Cancer Center, New York, said in a press briefing held in advance of the annual meeting of the American Society of Clinical Oncology.

"CBT-I is a highly effective therapy and can be considered the gold standard of treatment," he noted. However, this modality may be limited by poor adherence and nonresponse. Moreover, it is highly specialized and not currently available in many cancer centers or communities.

Functional imaging studies have shown that acupuncture can regulate brain regions involving cognition and emotion that are essential to sleep regulation, and clinical research has shown that it can improve pain- and hot flash–related sleep disturbances, according to Dr. Mao.

Main results of the CHOICE (Choosing Options for Insomnia in Cancer Effectively) trial showed that patients in both the CBT-I and acupuncture groups reduced their Insomnia Severity Index scores by more than one-half at the end of the 8-weeks treatment period, but the reduction was a statistically significant 2.6 points greater with CBT-I. Benefit of each treatment was still evident after 12 weeks.

Response rate was higher with CBT-I than with acupuncture only among patients having mild insomnia at baseline, and the two treatments yielded similar improvements in mental and physical quality of life.

"Among cancer patients with insomnia, we found that both acupuncture and CBT-I produced clinically meaningful and durable benefit, but overall, CBT-I is more effective in reducing insomnia severity," Dr. Mao concluded. "Our hope is that by doing this type of research, we can help patients and clinicians pick the right kind of treatment and help them to manage their sleep. Our next step is to really examine for what type of patient treatment would be beneficial, and how to deliver this type of effective treatment to the broader community of cancer patients."

Insomnia among cancer survivors is both prevalent and problematic, agreed ASCO President Bruce E. Johnson, MD, FASCO.

"The most common way we treat this is pharmacologically, with sleeping pills," he noted. "This trial shows that two different methods using something other than medications can help people with sleep, and not only do they help people with sleep, but they improve their quality of life, said Dr. Johnson, who is also a professor of medicine at the Dana-Farber Cancer Institute in Boston, and a leader of the center's lung cancer program.

The CHOICE trial did not have any restrictions on cancer type or stage; more than a half-dozen types were represented among the 160 patients enrolled, with breast cancer (31%) and prostate cancer (23%) accounting for the largest shares. The majority of patients were white (70%) and had moderate to severe insomnia (79%).

Patients were randomized to receive either acupuncture sessions (10 sessions, with points selected to treat insomnia plus comorbid symptoms such as fatigue and anxiety) or CBT-I (7 sessions), each over the course of 8 weeks.

Main results showed that, at the end of treatment, the reduction in Insomnia Severity Index was 8.3 points with acupuncture and 10.9 points with CBT-I ($P = .0007$), Dr. Mao reported. Benefit of each treatment was sustained after 12 weeks.

In stratified analysis, the rate of response (defined as a greater than 8-point reduction) was higher with CBT-I than with acupuncture among patients with mild insomnia (Insomnia Severity Index of 8-14) (85% vs. 18%; P less than .0001), but not among patients with moderate or severe insomnia (Insomnia Severity Index of 15 or higher) (75% vs. 66%; $P = .26$).

Dr. Mao disclosed no relevant conflicts of interest. The study received funding from the Patient-Centered Outcomes Research Institute.

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SOURCE: Mao JJ et al. ASCO 2018, Abstract 10001.

Black women more likely to have poor sleep quality

BY RICHARD MARK KIRKNER
MDedge News

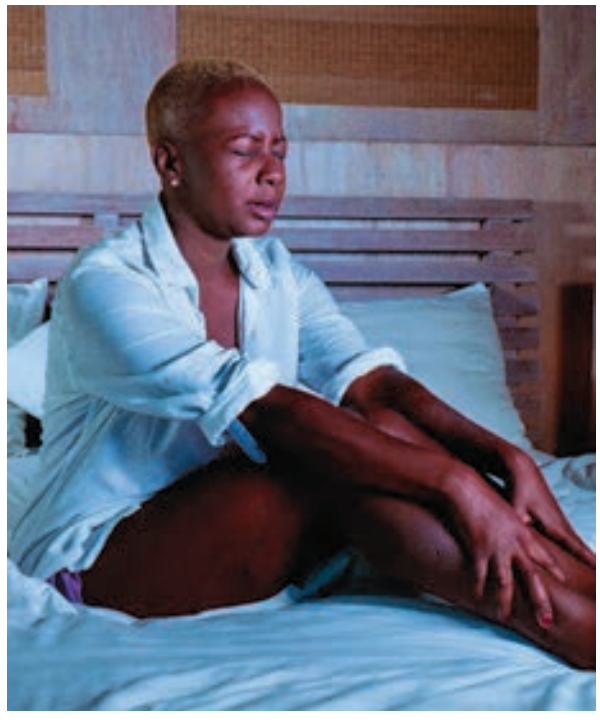
BALTIMORE – Analysis of data from a national multicenter study of women's health has found that middle-aged black women were at higher risk for sleep problems than their white counterparts, according to a presentation at the annual meeting of the Associated Sleep Societies.

"Race is emerging as a significant moderator in the relationship between sleep and health outcomes," said Marissa Bowman, a doctoral student at the University of Pittsburgh. The study was based on 10- to 15-year follow-up data from the SWAN (Study of Women's Health Across the Nation) sleep research. The researchers evaluated sleep in 265 midlife women, 45% of whom were black.

She noted that black women in the study were more likely to have poor sleep quality as assessed by Pittsburgh Sleep Quality Index, shorter sleep duration as assessed by polysomnography, longer periods of wakefulness after sleep onset, shorter sleep efficiency, and apnea-hypopnea index greater than 15. The study evaluated six factors of sleep quality: regularity, satisfaction, alertness, timing, efficiency, and duration.

At baseline, the study assessed sleep health using both actigraphy and a daily diary, along with body mass index, waist circumference (WC), and waist-to-hip ratio (WHpR), then collected data on the anthropometric factors 10-15 years later.

Cross-sectional and prospective analyses found that sleep health was correlated with lower BMI but was not significantly associated with WC or WHpR. A prospective analysis found no overall significant correlation between sleep health and any of the three factors. But in a separate analysis of the study group by race, all three anthropometric factors had a stronger link to sleep health in black women than in those of European descent, respectively, with beta coefficients of –0.14 vs. 0.1 for BMI, –0.17 and 0.1 for WC and –0.17 and 0.07 for WHpR.



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"We need to explain this association and conceptualize how sleep health might be more strongly related with weight in African Americans," Ms. Bowman said. "One possibility might be that sleep health reflects a health disparity. We can see how race is related to other health disparities, and this might be one of them."

During questions, Ms. Bowman acknowledged that SWAN did not have data on what kind of access to health care the black women in the study had. "That might be a possible reason they're not getting their sleep treated; they're not getting other health factors treated," she said.

Ms. Bowman and her coauthors reported no financial relationships. The study was funded by the National Institute on Aging, National Institutes of Health, and the National Institutes of Health Office of Research on Women's Health.

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OSA with hypoxemia raises metabolic syndrome risk

BY RICHARD MARK KIRKNER
MDedge News

BALTIMORE – An 8-year cohort study has found that patients with obstructive sleep apnea who are prone to worsening of hypoxemia at night have a heightened risk of developing metabolic syndrome, an investigator reported at the annual meeting of the Associated Professional Sleep Societies.

"Considering that we have a very high prevalence of moderate to severe obstructive sleep apnea (OSA) in the general population, this is a very important finding because it indicates that we need some clinical options of treating OSA in those that have metabolic syndrome to decrease the risk of morbidity and mortality and cardiac events in these patients," said Camila Hirotsu, PhD, of the Federal University of São Paulo.

Dr. Hirotsu presented 8-year follow-up results of the EPISONO cohort, an observational prospective study conducted in Brazil, the goal of which was to evaluate how OSA can impact the risk of developing metabolic syndrome (MetS) in the general population. MetS is defined as a cluster of three or more cardiovascular metabolic components: low HDL levels, high glucose and triglycerides, hypertension, and abdominal obesity. Dr. Hirotsu said that 50%-60% of MetS patients have OSA (PLoS One. 2010;5:e12065).

The study enrolled 1,074 patients at baseline, closing enrollment in 2008, and obtained follow-up on 712, evaluated from July 2015 to April 2016. After exclusions, the study evaluated 476 patients who were free of MetS at baseline. Of those 476, 44% went on to develop MetS.

Median age of patients who developed MetS was 40.8 years vs. 36.1 for those who did not. Patients who developed MetS also had a higher body mass index, but were not obese: 26.9 kg/m^2 vs. 23.8 kg/m^2. Patients were evaluated by completing questionnaires, undergoing full polysomnography, and having clinical assessments.

Patients with moderate to severe OSA were found to have an odds ratio of 2.47 (P = .016) of developing incident MetS, Dr. Hirotsu said. Rates of moderate to severe OSA were 21.3% for the group that devel-

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oped MetS versus 9% for the non-MetS group, said Dr. Hirotsu.

The study determined that the following sleep changes were associated with incident MetS: apnea-hypopnea index (AHI) (OR, 1.16); 3% oxygen desaturation index (ODI) (OR, 1.24); and time with oxygen saturation by pulse oximeter (SpO2) less than 90% (OR, 1.42).

Patients with moderate to severe OSA were found to have an odds ratio of 2.47 of developing incident metabolic syndrome. Rates of moderate to severe OSA were 21.3% for the group that developed MetS vs. 9% for the non-MetS group.

"Moderate to severe OSA at baseline and worsening of nocturnal hyperemia from baseline to follow-up are really independent risk factors to increase the incidence of MetS in the general population," Dr. Hirotsu explained.

A secondary aim of the study was to evaluate the impact of MetS on the risk of developing OSA in the general population. "It seems that MetS is not really an independent risk factor for OSA."

Dr. Hirotsu reported having no conflicts of interest.

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Waning vaccine immunity linked to pertussis uptick

BY BIANCA NOGRADY
MDedge News

The resurgence of whooping cough in the United States could be the result of waning pertussis immunity combined with incomplete historical coverage, researchers said.

Researchers reported in Science Translational Medicine on a study that used different models of transmission to explore what might be the cause of the steady increase in pertussis infections since the mid-1970s. "We considered whether pertussis vaccines failed to confer immunity in some recipients whether vaccine-induced immunity waned with time; and whether vaccines may have induced some, but imperfect, protection against the disease," they wrote.

The three modes of vaccine failure modeled in the study were primary vaccine failure in a fraction of the population; waning of vaccine-induced protection over time; and failure in the degree of protection offered by the vaccine, perhaps caused by antigenic evolution in the pertussis bacteria

Using 16 years' worth of detailed, age-stratified incidence data from Massachusetts, researchers found that the model which assumed a gradual waning in protection was the best fit for the observed patterns of pertussis incidence across the population.

Individuals who either did not get vaccinated as children or who did not gain immunity from vaccination were growing to adulthood without ever being exposed to natural infection.

This model suggested significant variability in how the level of protection changes over time, with a 10% risk of vaccine protection waning to zero within 10 years of completing routine vaccination and a 55% chance that the vaccine would confer lifelong protection.

"Crucially, we find that the vaccine is effective at reducing pathogen circulation but not so effective that eradication of this highly contagious bacterium should be possible without targeted booster campaigns," wrote Dr. Matthieu Domenech de Cellès, PhD, of the Institut Pasteur at the University of Versailles (France) and his coauthors.

The model also considered the possibility that the whole-cell and acellular pertussis vaccines might show differences in immunity, which had been suggested as one explanation for the resurgence of the disease. However, the authors found little evidence of a marked epidemiological switch from the whole-cell to acellular vaccines, although their results did suggest the acellular vaccine has a moderately reduced efficacy.

"Our results suggest that the train of events leading to the resurgence of pertussis was set in motion well

Continued on following page

Cash, not e-cigarettes, helped patients stop smoking

BY RANDY DOTINGA
MDedge News

A new study finds it pays to pay people to stop lighting up: Smokers were more likely to quit if they had an opportunity to gain rewards worth $600 than if they simply received free cessation aids or free e-cigarettes.

The wide majority of the more than 6,000 smokers in the randomized study didn't quit despite offers of various incentives. All the same, "programs that offered financial incentives tripled the rates of smoking cessation, reduced employers' costs per successful quit, as compared with programs that offered cessation aids alone, and yielded total costs that compared favorably with the costs of employing smokers," the study authors wrote.

The study, led by Scott D. Halpern, MD, PhD, of the University of Pennsylvania, was published online May 23 in the New England Journal of Medicine.

The researchers reached out to employees and spouses at 54 companies that use wellness programs provided by the Vitality Institute, which supports research into health promotion. The institute provided grant support for the study.

Just over 6,000 employees and spouses who smoked were assigned to five groups. One group received usual care. The others received interventions: free smoking-cessation aids (nicotine replacement therapy, bupropion, or varenicline); free e-cigarettes; up to $600 worth of an unidentified "reward incentive" plus free cessation aids; and up to $600 via a redeemable deposit, plus free cessation aids.

Participants could get the entire reward incentive or the full $600 redeemable deposit only if they showed signs of sustained smoking cessation via blood or urine test at 1, 3, and 6 months.

'Programs that offered financial incentives tripled the rates of smoking cessation, reduced employers' costs per successful quit, as compared with programs that offered cessation aids alone, and yielded total costs that compared favorably with the costs of employing smokers.'

artisteer/Getty Images

The median age in the groups ranged from 43 to 45 years, and most were not college graduates. Just over half were women, and roughly 90% said they wanted to quit smoking.

Overall, 20% of the 6,006 participants logged onto the trial website, a sign that they were "engaged." The number was highest in the free e-cigarette and reward groups (21%-23%) and lowest in the usual-care group (16%).

The researchers focused on how many participants abstained from smoking – as confirmed by blood or urine test – for 6 months past the target quit date. The test data confirmed that just 1.3% of the total participants, 80 people, sustained cessation over 6 months.

Only 0.1% of the usual-care group sustained smoking cessation, and the number wasn't much higher (0.5%) in the free cessation–aids group.

One percent of those in the free e-cigarette group sustained cessation. However, the researchers noted there wasn't a significant difference in the quit rates between the usual-care, free cessation–aid, and free e-cigarette groups.

"The observation of greater e-cigarette use in the free e-cigarette group than in the free cessation aids group, coupled with the absence of benefit of free e-cigarettes versus no intervention, supports the conclusion that offering free e-cigarettes does not promote smoking cessation," they cautioned.

In the reward incentive and $600 redeemable-deposit groups, 2% and 2.9% of participants quit over a sustained period, respectively. Cessation rates in the $600 deposit group were superior to the free cessation aid group (P less than .001) and the free e-cigarette group (P = .008). Cessation rates in the incentive group were superior to those in the free cessation–aid group (P = .006).

"Average costs per participant assigned to each intervention were lowest in the usual-care group ($0.82) and highest in the redeemable-deposit group ($100.96)," the researchers reported. "The overall cost of each program per participant who was abstinent for 6 months was lower in the rewards and redeemable-deposit groups than in the free e-cigarettes or free cessation aids groups."

The study received grant support from the Vitality Institute. Most of the study authors reported no relevant disclosures. One author reported serving on the scientific advisory board of VAL Health, and another reported various grants and personal fees.

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SOURCE: Halpern SD et al. N Engl J Med. 2018 May 23. doi: 10.1056/NEJMsa1715757.

Continued from previous page

before the shift to the DTaP vaccine," Dr. Domenech de Cellès and his associates said.

The model also pointed to big shifts in the age-specific immunological profile caused by introduction of vaccination, which led to a reduction in transmission and also a reduction in natural infections both in vaccinated and unvaccinated individuals.

This meant individuals who either did not get vaccinated as children or who did not gain immunity from vaccination were growing to adulthood without ever being exposed to natural infection.

"Concurrently, older cohorts, with their long-lived immunity derived from natural infections experienced during the prevaccine period, were gradually dying out," the authors said. "The resulting rise in the number of susceptible adults sets the stage for the pertussis resurgence, especially among adults."

Two authors were supported by the National Institutes of Health and by Models of Infectious Disease Agent Study–National Institute of General Medical Sciences. No conflicts of interest were declared.

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SOURCE: Domenech de Cellès M et al. Sci Transl Med. 2018 Mar 28;10:eaaj1748.

Methotrexate-induced pulmonary fibrosis risk examined in 10-year study

BY SARA FREEMAN
MDedge News

LIVERPOOL, ENGLAND – A 10-year follow-up of patients with inflammatory arthritis has shown that methotrexate does not appear to increase the risk of pulmonary fibrosis.

"It's a really important message that methotrexate does not cause chronic pulmonary fibrosis and it should not be stopped because of pulmonary fibrosis," Julie Dawson, MD, said in an interview at the British Society for Rheumatology annual conference. "It's the rheumatoid arthritis. It's not the methotrexate."

Dr. Dawson, of St. Helens and Knowsley Teaching Hospitals NHS Trust, St. Helens, England, added that the current findings were consistent with her team's prior research looking at earlier time periods. There was also no correlation between the duration or dose of methotrexate used and the development of the lung disease, she said.

If patients are not doing well on methotrexate, then perhaps adjusting therapy or changing to another drug would of course be the next step, but if patients are well controlled then "stopping it is the worst thing to do" for their arthritis, she said.

"This is of great clinical interest, and we can be reassured now about this, I think. This is really good, long-term data," said Devesh Mewar, MD, of Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, who was not involved in the research.

"We know that methotrexate is associated with a pneumonitis reaction, but there is no high-quality evidence that methotrexate is associated with a chronic pulmonary fibrosis" Dr. Dawson said, explaining the rationale for the current study she presented during a poster session. Previous studies considered data for up to 5 years, she added, so the aim of the current study, therefore, was to look at the longer-term effect of methotrexate use on the incidence of pulmonary fibrosis.

Data on 129 patients who had started treatment with methotrexate from 2004 to 2007 were analyzed, of whom 63 (49%) had stayed on methotrexate for 10 or more years. Most (82%) had been given methotrexate to treat rheumatoid arthritis, with other indications including inflammatory arthritis (5.4%) and psoriatic arthritis (4.7%).

Sara Freeman/MDedge News

Dr. Julie Dawson

"Practice was different 10 years ago, so just 56% of patients commenced methotrexate within the first year of the diagnosis of rheumatoid arthritis," Dr. Dawson reported.

Only four cases of symptomatic pulmonary fibrosis were seen, all in the RA patients, and three of these were in patients who had started methotrexate over 1 year after their diagnosis. The incidence of 3.8% seen in the study matches the expected incidence of pulmonary fibrosis in RA and was actually "at the lower end of the expected incidence," Dr. Dawson said. Previous studies have suggested an incidence rate of RA-associated interstitial lung disease of about 3%-7%.

All of the pulmonary fibrosis cases had occurred in men and 75% were seropositive for rheumatoid factor. The mean duration of RA at the time of onset of pulmonary fibrosis was 7.8 years, and the usual interstitial pattern of fibrosis was seen. The 125 patients without pulmonary fibrosis had taken methotrexate for a mean of 8 years at a mean final weekly dose of 16.3 mg, compared with a mean of 6 years at a mean dose of 18.1 mg per week in the 4 patients with pulmonary fibrosis.

One of the next steps is to look at cases where methotrexate has been stopped and the effects of that on pulmonary fibrosis and disease activity. In Dr. Dawson's experience, stopping methotrexate just affects the management of the arthritis and had no difference to the progression of pulmonary fibrosis.

If patients start to experience any lung symptoms while continuing methotrexate, such as shortness of breath, then they would need to be assessed and undergo lung function tests to monitor their condition. Treating the fibrosis using an antifibrotic drug, such as pirfenidone, is something that might be possible in the future, but this needs investigation in inflammatory arthritis as the drug is currently licensed for use only in idiopathic cases.

This is something the British Rheumatoid Interstitial Lung network plans to investigate in a placebo-controlled study of RA patients with fibrotic lung disease. "We're looking to see if antifibrotic agents are going to slow the disease as it does in idiopathic pulmonary fibrosis, which is obviously quite exciting when it's such a hard condition to treat," said Dr. Dawson, who will be one of the study's investigators.

Dr. Dawson had no conflicts of interest to disclose. Dr. Mewar was not involved in the study and had nothing to disclose.

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SOURCE: Dawson J et al. Rheumatology. 2018;57(Suppl. 3):key075.470.

VIEW ON THE NEWS

Study generates hypotheses but leaves incidence unknown

The subject of this retrospective study is of great interest. The authors point out that pulmonary fibrosis (as opposed to acute allergic reaction, which is extremely rare) is also extremely uncommon in patients using methotrexate over the long haul. Over 10 years, their data point to a 3.1% incidence of symptomatic pulmonary fibrosis.

The issue here is its generalizability. There were 63 patients who used methotrexate for 10 years or more and 88 who used it for 5 years or more, according to the poster. This must represent a highly selected population. For example, what percent of the total RA/psoriatic arthritis/"inflammatory arthritis" population do these patients represent; i.e., what is the denominator here? The authors stated that the 63 patients who stayed on methotrexate for 10 or more years represent 49% of the 129 patients on methotrexate overall in the study. This is a highly unusual datum, as most of the literature indicates that only 40% or less of patients stay on methotrexate for even 5 years. And this completely ignores the issue of adherence over this long a period; these patients must represent a truly minuscule percentage of the total if they actually stayed on methotrexate with even moderate adherence for 10 years.

Importantly, the authors point out that they had only four cases of symptomatic pulmonary fibrosis. Once more, this points to the highly selective group of patients seen, as this study does not examine patients with asymptomatic pulmonary fibrosis, including those with fibrosis on high-resolution CT of the lungs or chest film or evidence of abnormalities on pulmonary function tests, but who do not have sufficient symptoms ascribed to methotrexate to bring them to medical attention.

This is a nice hypothesis-generating study, but the actual incidence of methotrexate-induced lung fibrosis remains completely unknown. I heartily applaud their intention to start a prospective study to answer this interesting question.

Daniel E. Furst, MD, is professor of rheumatology at the University of Washington, Seattle, who also is affiliated with the University of California, Los Angeles, and the University of Florence (Italy). He was not involved with the study.

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Aclidinium bromide for COPD: No impact on CV events

BY DOUG BRUNK
MDedge News

SAN DIEGO – The use of aclidinium bromide 400 mcg b.i.d. did not increase the risk of major adverse cardiac events or mortality in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) with significant cardiovascular risk factors, compared with placebo.

Those are two key findings from the ASCENT COPD trial presented by Robert A. Wise, MD, FCCP, at an international conference of the American Thoracic Society. "Cardiovascular risk factors and comorbidities are prevalent in patients with COPD, and about 30% of COPD patients die of cardiovascular disease," said Dr. Wise, who serves as director of research for the division of pulmonary and critical care medicine at the Johns Hopkins University School of Medicine, Baltimore. "However, patients who have cardiovascular disease are often excluded from, or not enrolled in, COPD clinical trials. Moreover, there has been controversy as to whether or not treatment with a long-acting muscarinic antagonist is associated with an increased risk of cardiovascular events. That's been seen in randomized trials, meta-analyses, as well as in observational studies."


DR. WISE

Aclidinium bromide 400 mcg b.i.d., administered by the Pressair inhaler, is approved as a maintenance treatment for patients with COPD. However, during the registration studies, there were not an adequate number of cardiovascular events in order to ascertain clearly whether or not the drug was associated with increased risk, Dr. Wise said. Therefore, he and his associates in the ASCENT COPD study set out to assess the long-term cardiovascular safety profile of aclidinium 400 mcg b.i.d. in patients with moderate to very severe COPD at risk of major adverse cardiovascular events (MACE) for up to 3 years (Chronic Obstr Pulm Dis. 2018;5[1]:5-15). For the randomized, placebo-controlled, parallel-group study, patients received treatment with aclidinium bromide or a placebo inhaler of similar appearance. The study was designed to be terminated when at least 122 patients experienced an adjudicated MACE. The primary safety endpoint was time to first MACE during follow-up of up to 3 years, while the primary efficacy endpoint was the rate of moderate to severe exacerbations per patient per year during the first year of treatment.

To be included in the study, patients had to be at least 40 years of age with moderate to very severe stable COPD, have a smoking history of at least 10 pack-years, and have at least one of the following significant risk factors: cerebrovascular disease;

Continued on following page

Phase 2a trial: Investigational drug delivered significant bronchodilation in two-week study

BY DOUG BRUNK
MDedge News

SAN DIEGO – The investigational agent AZD8871 at once-daily doses of 100 mcg and 600 mcg led to statistically significant, clinically relevant, and dose-ordered differences in trough forced expiratory volume (FEV_1) at 2 weeks, compared with placebo, results from a phase 2a trial showed.

AZD8871 is a long-acting, bifunctional bronchodilator that combines a muscarinic antagonist and a $beta_2$ adrenoceptor agonist. "There are some interesting avenues that you can explore with such a molecule," one of the study authors, Dave Singh, MD, said at an international conference of the American Thoracic Society. "First, theoretically, as a single molecule you will be able to deposit both the active ingredients to the same site in the lung. On a more practical note, if you want to add something else to a dual bronchodilator, which is essentially what AZD8871 is, this provides a platform. Perhaps that's the most interesting use of this type of approach."

Single doses of AZD8871 (400 mcg and 1,800 mcg) administered in chronic obstructive pulmonary disease (COPD) patients demonstrated sustained bronchodilation over 36 hours. In a study presented at the 2017 meeting of the European Respiratory Society, Dr. Singh and his associates found that AZD8871 1,800 mcg showed greater bronchodilation than both indacaterol and tiotropium for peak and trough FEV_1.

For the current study, researchers at one site in the United Kingdom and one site in Germany conducted a phase 2 randomized, double-blind, placebo-controlled trial of AZD8871 in 42 patients aged 40-80 years with moderate to severe reversible COPD. Patients were randomized to receive repeated once-daily doses of AZD8871 100 mcg, 600 mcg, or placebo via a dry powder inhaler device for 14 days. Between-treatment washout periods were 28-35 days. "We keep the patients in-house on day 1 and day 14 of each treatment period, and we measure lung function over 24 hours," said Dr. Singh, professor of clinical pharmacology and respiratory medicine at the University of Manchester (England). "Patients were allowed to continue any preexisting steroid therapy, but at the end of screening they had to withdraw any long-acting bronchodilator therapy."

Doug Brunk/MDedge News

Dr. Dave Singh discussed phase 2a trial results for AZD8871, an investigational agent.

The primary efficacy endpoint was change from baseline trough FEV_1 on day 15. Secondary endpoints included change from baseline in peak FEV_1, total score of breathlessness, cough, sputum scale questionnaire, and rescue medication use.

At baseline, the mean age of the 42 patients was 64 years, and 67% were male. Their mean FEV_1 was about 58% predicted, and their FEV_1 absolute reversibility was a mean of 379 mL, "which is rather high," he said.

Of the 42 randomized patients, 31 completed all three treatments. Both doses of AZD8871 had a positive, dose-dependent effect on FEV_1, compared with placebo, and both doses demonstrated an onset of action within 15 minutes. On day 15, least square mean change from baseline differences in trough FEV_1 for AZD8871 100 mcg and 600 mcg versus placebo were 161 mL and 260 mL, respectively.

A similar association was observed with peak FEV_1, which between baseline and day 14 increased by 380 mL at the 100-mcg dose and by 420 mL at the 600-mcg dose, compared with placebo. Sustained bronchodilation was observed over 24 hours on both day 1 and day 14.

Statistically significant COPD symptom improvements, measured by breathlessness, cough and sputum scale (BCSS), were observed for AZD8871 600 mcg on day 8 (P = .002) and day 14 (P less than .001), compared with placebo.

In addition, substantial symptomatic improvements were observed for AZD8871 600 mcg on day 14 versus placebo (least square mean of –1.16). Similar results were observed for individual domains of the BCSS. "When you separate out the different components of the scale, most of this is driven by the change in breathlessness," he said. "We were surprised that we could capture this in such a small number of patients."

On days 1-8 and days 9-14, the researchers observed a statistically significant improvement in change from baseline rescue medication use for AZD8871 600 mcg (P less than 0.001) and 100 mcg (P = .029 and P = .012, respectively), compared with placebo.

The most common adverse events for patients in all three treatment groups were headache (21.4%) and worsening of COPD-related symptoms (14.3%). No dose dependence was observed with any adverse event, including serious adverse events and/or those leading to discontinuation.

AstraZeneca, the developer of AZD8871, sponsored the study. Dr. Singh reported being a consultant to and receiving research support from AstraZeneca and numerous other pharmaceutical companies.

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SOURCE: Singh D. et al. ATS 2018, Abstract 7708.

Continued from previous page

coronary artery disease; peripheral vascular disease, or history of claudication; or at least two atherothrombotic risk factors (male at least 65 years of age, female at least 70 years of age; waist circumference of at least 40 inches among males or at least 38 inches among females; an estimated glomerular filtration rate of less than 60 mL/min and microalbuminuria; dyslipidemia; or hypertension).

The researchers randomized 1,791 patients to the aclidinium group and 1,798 to the placebo group. Their mean age was 67 years, and about 60% of patients had an exacerbation in the preceding year. Nearly two-thirds of patients (63%) were receiving concomitant long-acting $beta_2$-agonists (LABA) or LABA/inhaled corticosteroid therapy. In addition, 44% of patients entered the study with a history of a prior cardiovascular event plus at least two atherothrombotic risk factors, 52% reported at least two atherothrombotic risk factors without any prior cardiovascular events, and 4% had a history of a prior cardiovascular event only.

The ASCENT COPD study set out to assess the long-term cardiovascular safety profile of aclidinium 400 mcg b.i.d. in patients with moderate to very severe COPD at risk of major adverse cardiovascular events, or MACE, for up to 3 years.

Dr. Wise reported that aclidinium did not increase the risk of MACE in patients with moderate to very severe COPD with significant cardiovascular risk factors, compared with placebo (hazard ratio 0.89; P = .469); noninferiority was concluded as the upper bound of the 95% confidence interval was less than 1.8). In terms of all-cause mortality, aclidinium did not increase the risk of death, compared with placebo (HR, 0.99; P = .929).

During the first year of treatment, Dr. Wise and his associates also observed a 22% reduction in COPD exacerbation rate for aclidinium vs. placebo groups (HR, 0.44 vs. 0.57, respectively; P less than .001), and a 35% reduction in the rate of COPD exacerbations leading to hospitalizations (HR, 0.07 vs. 0.10; P = .006). "The reduction in exacerbation risk was similar, whether or not patients had an exacerbation in the past year," Dr. Wise said. He reported being a consultant to, and receiving research support from, AstraZeneca, Boehringer Ingelheim, ContraFect, and GlaxoSmithKline.

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SOURCE: Wise R. et al. ATS 2018, Abstract 7711.

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THE ELIQUIS STARTER PACK
Designed to support DVT/PE treatment initiation

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IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.
  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

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DVT=deep vein thrombosis; PE=pulmonary embolism.

WARNINGS AND PRECAUTIONS (cont'd)

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

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

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

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

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

DRUG INTERACTIONS

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

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

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

- **Refill reminder:** prompts DVT/PE patients to refill their ELIQUIS prescription

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INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

Please see Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on the following pages.

432US1800647-02-01 03/18

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

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

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery— ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

A specific antidote for ELIQUIS is not available, and there is no established way to reverse the bleeding in patients taking ELIQUIS. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

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

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

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

ADVERSE REACTIONS

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

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions]*

Clinical Trials Experience

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

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

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

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

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

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

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

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

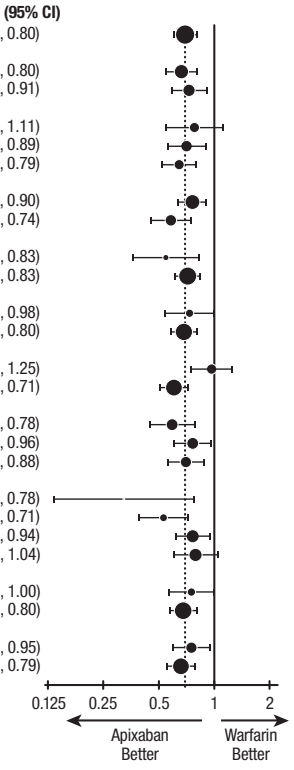
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

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

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

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

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

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

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

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

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

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

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

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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and
Pfizer Inc
New York, New York 10017 USA

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Custom-made 3-D stents created for anatomically complex airway stenosis

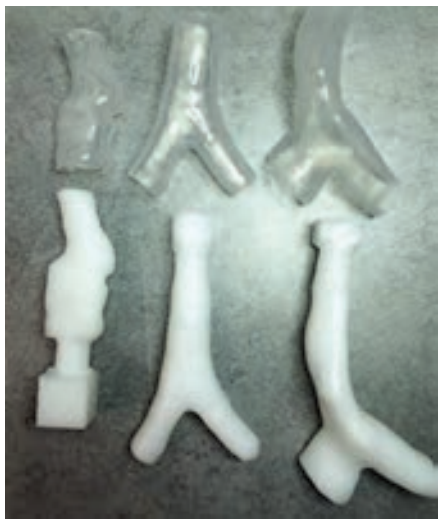
BY DOUG BRUNK
MDedge News

SAN DIEGO – Customized airway stents made from 3-dimensional imaging software provided compelling outcomes in patients with nonmalignant, anatomically complex, and symptomatic stenosis for whom conventional stents were not suitable or failed, results from a small study demonstrated.

"Anatomically complex airway stenosis remains a challenging situation," lead study author Nicolas Guibert, MD, said at an international conference of the American Thoracic Society. "Conventional devices are either not suited or may result in a significant complication rate, including poor clinical tolerance, migration, or granulation tissue reaction due to lack of congruence."

Dr. Guibert, a pulmonologist at Toulouse (France) University Hospital, and his associates hypothesized that patient-specific, fully customized 3-D stents created by computer-assisted design has the potential for improving tolerance and decreasing the complication rate. In a feasibility study, they recruited 10 patients with nonmalignant, anatomically complex, and symptomatic stenosis for whom conventional stents were not suitable or failed. After computer-assisted segmentation of the airways from a CT scan and virtual relief of the stenosis, a virtual 3-D stent and corresponding mold was designed for each patient, a process that takes 3-4 weeks, including sterilization. Numerical data were then entered into a 3-D computer numeric control machine to produce the Ertacetal mold, from which the silicon stent is made. The researchers placed the stents under general anesthesia through rigid bronchoscopy and collected data on complication rate, dyspnea as defined by the New York Heart Association classification, quality of life as defined by the VQ11 measure, and respiratory function at day 7 and at 3, 6, and 12 months. Congruence of the stent was assessed preoperatively via bronchoscopy and at 1 week via CT scan.

'Conventional devices are either not suited or may result in a significant complication rate, including poor clinical tolerance, migration, or granulation tissue reaction due to lack of congruence.'



COURTESY DR. NICOLAS GUIBERT

A virtual 3-D stent and corresponding mold was designed for each patient.

Dr. Guibert reported results from several patients. Of these, three had posttransplant complex airway stenoses involving the bronchus intermedius. Each improved after placement of the customized stents. For example, one patient with vanishing bronchus intermedius syndrome experienced improvements in NYHA dyspnea score from 3 to 1, the VQ11 score from 22 to 11/55, and forced expiratory volume in 1 second (FEV_1) from 70% to 107%. The stent was removed after 3 months. Meanwhile, a patient with localized malacia and stenosis of the right main bronchus experienced improvements in NYHA dyspnea score from 3 to 1, VQ11 score from 27 to 15/55, and FEV_1 from 70% to 102%. That person's stent is still in place with no complications. Another patient with localized malacia and stenosis of the bronchus intermedius experienced improvements in FEV_1 from 84% to 100%. That person's device was removed after 3 months, with no residual stenosis.

A fourth patient underwent stent placement for localized malacia (cartilage ring rupture). That person experienced improvements in NYHA dyspnea score from 3 to 1, VQ11 from 23 to 15/55, and FEV_1 from 66% to 92%, and peak flow from 49% to 82%. The device is still in place with no complications. A fifth patient received stent placement for extensive tracheobronchomalacia, but it had imperfect congruence and was removed after 3 months because it caused intense cough.

One patient with posttracheotomy stenosis experienced improvements in NYHA dyspnea score from 3 to 0, VQ11 from 29 to 12/55, and peak flow from 45% to 81%. That person's device is still in place, Dr. Guibert said. Two other patients treated for posttracheotomy experienced stent migration (conventional stents also migrated in these two cases), despite good bronchoscopic congruence after placement.

Dr. Guibert reported having no financial disclosures.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As discussed in the article, significant symptoms related to anatomic airway abnormalities affect the daily lives of some patients in a major way. Unfortunately, for a large proportion of them airway interventions yield variable results and often ones that wane with time. Efforts to improve the options available for these patients are very much welcomed – since for many of them there is often little to offer. Another aspect in the care of these patients reflected by this work recognizes that a given modality for one patient may not be optimal for another, and the personalization of a given intervention may be equally as important.

Women still underrepresented in cardiovascular trials

BY ANDREW D. BOWSER
MDedge News

Women remain underrepresented in studies of heart failure, coronary artery disease, and acute coronary syndrome, a recent study authored by Food and Drug Administration researchers has revealed.

Representation was favorable in trials of drugs treating hypertension, atrial fibrillation, and pulmonary arterial hypertension, authors of the study wrote in the Journal of the American College of Cardiology.

However, representation of women fell below an acceptable participation-to-prevalence ratio in several critical categories of heart disease, according to researchers, including lead author Pamela E. Scott, PhD, of the FDA's Office of Women's Health.

To quantify the participation of women in clinical trials, Dr. Scott and coinvestigators reviewed publicly available FDA reviews from 2005 to 2015 supporting the approval of 36 drugs. They used a metric called the participation-to-prevalence ratio (PPR) to compare representation of women in a study relative to the representation of women in the disease population being studied. The range of PPR of 0.8-1.2 represented similar representation of women in the study and disease population.

A PPR of less than 0.8 was found for coronary artery disease trials, at 0.6; acute coronary syndrome/myocardial infarction trials, also at 0.6; and heart failure trials, at 0.5-0.6. Participation of women in drug trials varied widely – from a low of 22% to a high of 81% – with a mean of 46%, they found.

The PPR was within the desirable range for hypertension, at 0.9, and atrial fibrillation trials, at 0.8-1.1, while participation for pulmonary arterial hypertension trials was above the desirable range, at 1.4, according to the report.

Dr. Scott and coauthors reported that they had no relationships relevant to their study.

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SOURCE: Scott PE et al. J Am Coll Cardiol. 2018 May 18;71:1960-9.

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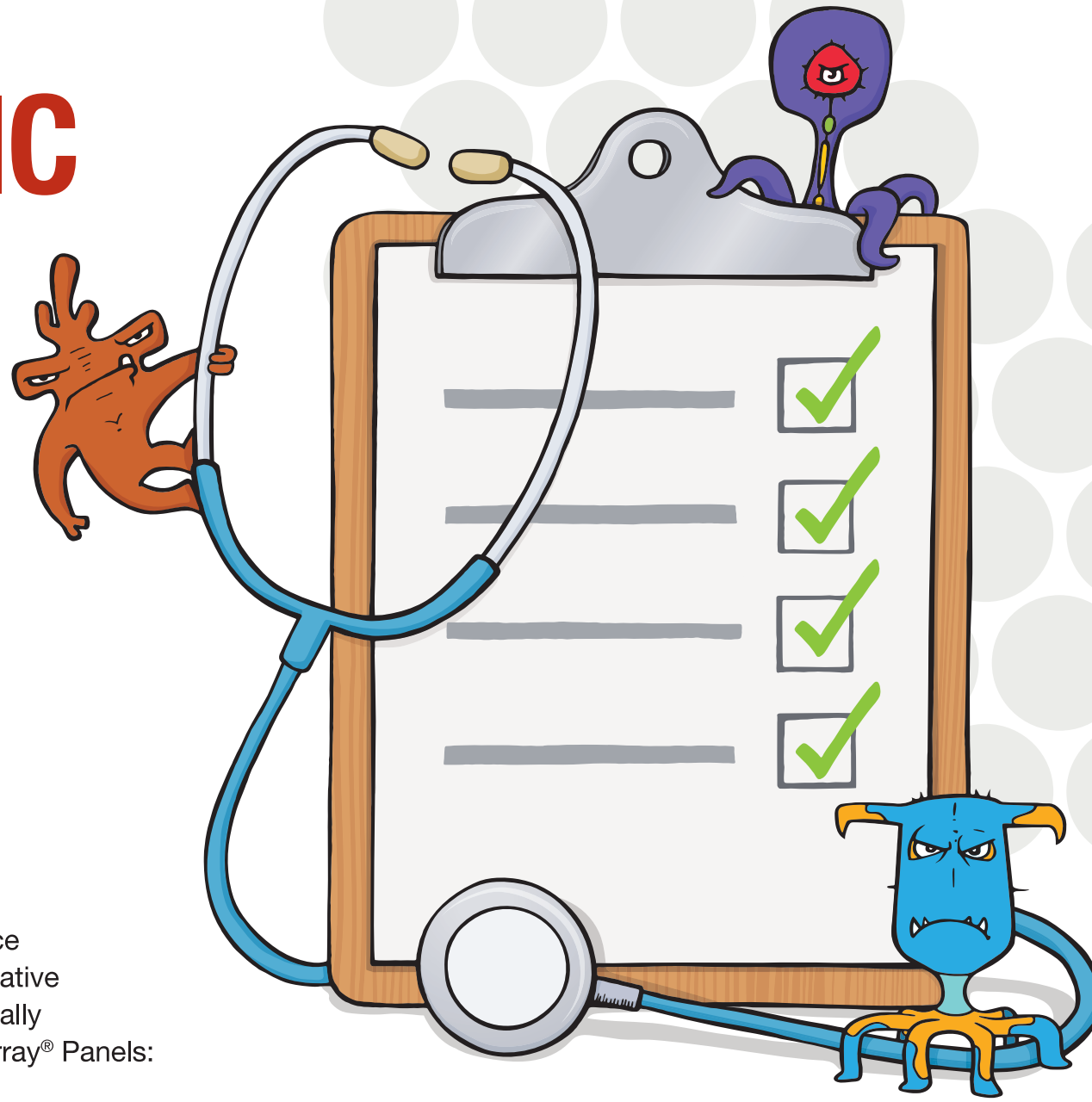

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Reversal agent for apixaban, rivaroxaban approved

BY CATHERINE HACKETT
MDedge News

Andexanet alfa, the first agent shown to reverse the anticoagulant effects of rivaroxaban and apixaban, has been approved by the Food and Drug Administration, according to a May 3 statement from Portola Pharmaceuticals.

It is approved for use in patients treated with these factor Xa inhibitors when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding, according to the company.

Andexanet alfa (Andexxa, Portola) received both U.S. Orphan Drug and FDA Breakthrough Therapy designations and was approved under the Food and Drug Administration's Accelerated Approval pathway.

"Today's approval represents a significant step forward in patient care and one that the medical community has been eagerly anticipating," said Stuart J. Connolly, MD, professor of medicine and an electrophysiologist at McMaster University in Hamilton, Ont., who is chair of the ANNEXA-4 executive committee. "Andexxa's rapid reversal of the anticoagulating effects of rivaroxaban and apixaban will help clinicians treat life-threatening bleeds, where every minute counts," he added in the statement.

The approval was supported by two phase 3 trials in the ANNEXA series, which showed acceptable change from baseline in anti-Factor Xa activity in healthy volunteers. But the strongest data came from interim results from ANNEXA-4, a single-arm cohort study with 227 patients who were receiving a factor Xa inhibitor and were experiencing an acute major bleeding event.

Clinicians administered andexanet alfa as a bolus followed by a 2-hour continuous infusion, with hemostatic efficacy assessed 12

'Andexxa ... will help clinicians treat life-threatening bleeds, where every minute counts.'

DR. CONNOLLY

hours after the start of treatment. The results showed that factor Xa inhibition fell by a median 90% for rivaroxaban and 93% for apixaban.

Andexanet alfa is a factor Xa "decoy" molecule that acts by latching onto the inhibitor molecules and thereby preventing them from interacting with actual factor Xa, but andexanet also has a short half-life and hence the effect quickly reduces once treatment stops, Dr. Connelly reported at the American College of Cardiology annual meeting in March when presenting ANNEXA-4.

He noted at the time the results placed andexanet in the same ballpark for efficacy and safety as idarucizumab (Praxbind) approved in 2015 for reversing the anticoagulant dabigatran (Pradaxa).

"The expansion of available reversal agents for people prescribed newer oral anticoagulant therapies is crucial," Randy Fenninger, CEO of the National Blood Clot Alliance, said in the Portola statement. "The availability now of a reversal agent specific to rivaroxaban and apixaban expands choice and enables patients and providers to consider these treatment options with greater confidence."

The prescribing information for andexanet states that treated patients should be monitored for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. Further, anticoagulant therapy should be resumed as soon as medically appropriate following andexanet treatment to reduce thromboembolic risk.

The most common adverse reactions, occurring in at least 5% of patients, were urinary tract infections and pneumonia.

Portola intends to bring Andexxa to limited markets in early June; a broader commercial launch is anticipated in early 2019.

The FDA is requiring a postmarketing clinical trial that randomizes patients to either andexanet or usual care. The study is scheduled to begin in 2019 and report outcomes in 2023.

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VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: The use of newer oral anticoagulants has facilitated the care of many patients in need of anticoagulants, but the lack of a reversal agent, unlike warfarin, has led to major difficulties in cases where emergency surgical interventions are required. This report is welcome news for the medical community caring for these patients.

Nebivolol most effective beta-blocker for hypertension

BY BRUCE JANCIN
MDedge News

ORLANDO – The use of nebivolol as part of a multidrug regimen to treat hypertension was associated with a significantly lower cardiovascular event risk than was combination antihypertensive therapy featuring either metoprolol or atenolol in a large observational study, Brent M. Egan, MD, reported at the annual meeting of the American College of Cardiology.

This retrospective study used health insurance claims data within the massive PharMetrics national U.S. database for 2007-2014 in order to identify 16,787 patients who started on nebivolol as part of a multidrug regimen for hypertension. They were aggressively propensity score–matched on the basis of demographics, clinical characteristics, and duration of follow-up to 16,787 hypertensive individuals on either metoprolol succinate or metoprolol tartrate as part of combination therapy, and to another 16,787 patients who started on atenolol for the same reason.

Patients averaged 53 years of age in all three groups. Importantly, this was a primary prevention study: None of the participants had a baseline history of any cardiovascular event.

The primary outcome was hospitalization for acute MI, stroke, heart failure, or angina during a mean 600 days of follow-up. In a Cox proportional hazards regression analysis, the risk of the composite outcome was 1.33-fold greater with atenolol and 1.91-fold greater with metoprolol than in the group on nebivolol for their hypertension.

Since nebivolol is a vasodilatory beta-blocker and atenolol and metoprolol are not, the investigators hypothesized that this distinction could result in differences in cardiovascular event rates.

The risk of hospitalization for MI was 1.47-fold greater in the atenolol group and 2.19-fold greater with metoprolol than in patients on nebivolol. Hospitalization for angina was 2.18 times more likely in the atenolol group and 3.39 times more likely in the metoprolol group than in patients on nebivolol. However, there was no between-group difference between the three beta-blockers in terms of stroke or heart failure rates, according to Dr. Egan of the University of South Carolina, Greenville.

He explained that the impetus for this study was that, even though beta-blockers are universally recognized as a cornerstone of secondary cardiovascular prevention, there are much fewer outcome data to support their use in primary prevention. Since nebivolol is a vasodilatory beta-blocker and atenolol and metoprolol are not, Dr. Egan and his coinvestigators hypothesized that this distinction could result in differences in cardiovascular event rates.

One audience member commented, "this study gives a nice hypothesis-generating rationale for doing a large randomized outcomes trial." Dr. Egan concurred.

His study was supported by Allergan. He reported receiving research grants from Boehringer Ingelheim and serving as a consultant to Medtronic.

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SOURCE: Egan BM et al. ACC 18, Abstract 1324M-11.

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Do you know what's driving her **severe asthma?**

AstraZeneca

Biomarkers elevated in children with LRTIs

BY DOUG BRUNK
MDedge News

TORONTO – While C-reactive protein, procalcitonin, and proadrenomedullin are associated with development of severe clinical outcomes in children with lower respiratory tract infections (LRTI), proadrenomedullin is most strongly associated with disease severity, preliminary results from a prospective cohort study showed.

"Despite the fact that pneumonia guidelines call the site of care decision the most important decision in the management of pediatric pneumonia, no validated risk stratification tools exist for pediatric lower respiratory tract infections," lead study author Todd A. Florin, MD, said at the annual Pediatric Academic Societies meeting. "Biomarkers offer an objective means of classifying disease severity and clinical outcomes."

Three frequently studied blood biomarkers in adults with LRTI by risk stratification are C-reactive protein (CRP), procalcitonin (PCT), and midregional proadrenomedullin (proADM). CRP is secreted by hepatocytes stimulated by interleukin (IL)-6, IL-1 beta, and tumor necrosis factor (TNF) alpha in response to inflammation and infection. "Elevation of CRP and the failure of CRP to fall over the course of treatment has been shown to be associated with adverse outcomes and severity scores, but not mortality in adults with lower respiratory tract infections," said Dr. Florin, a pediatric emergency physician at Cincinnati Children's Hospital.


Doug Brunk/MDedge News

'I do not anticipate that any single biomarker will be the magic bullet for predicting disease severity in pediatric CAP. It will likely be a combination of clinical factors and several biomarkers that will achieve optimal prognostic ability. That said, our results suggest that similar to adult studies, proADM appears to have the strongest association with severe disease.'

DR. TODD A. FLORIN

PCT and CPT link to LRTIs

PCT is a precursor of calcitonin secreted by the thyroid, lung, and intestine in response to bacterial infections. It also has been shown to be associated with adverse outcomes and mortality in adults, with results generally suggesting that it is a stronger predictor of severity than CRP.

"There is limited data on the association of CRP or PCT with severe outcomes in children with LRTIs," Dr. Florin noted. "One recent U.S. study of 532 children did demonstrate an association of elevated PCT with ICU admission, chest drainage, and hospital length of stay in children with CAP [community-acquired pneumonia]."

ProADM, meanwhile, is a vasodilatory peptide with antimicrobial and anti-inflammatory functions synthesized during severe infections. It has a half-life of several hours and has been shown to be associated with disease severity in adults with LRTI. Recent studies have shown that it has improved prognostication over WBC, CRP, and PCT. "

Dr. Florin said, "Although all three of these markers demonstrate promise in predicting severe outcomes in adults with LRTIs, very few studies have examined their association with disease severity in pediatric disease. Therefore, the aim of the current analysis was to determine the association between blood biomarkers and disease severity in children who present to the ED with lower respiratory tract infections."

The CARPE DIEM study

In a study known as Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine (CARPE DIEM), he and his associates performed a prospective cohort analysis of children with suspected CAP who were admitted to the Cincinnati Children's Hospital ED between July 2012 and December 2017. They limited the analysis to children aged 3 months to 18 years with signs and symptoms of an LRTI, and all eligible patients were required to have a chest radiograph ordered for suspicion of CAP. They excluded children hospitalized within 14 days prior to the index ED visit, immunodeficient or immunosuppressed children, those with a history of aspiration or aspiration pneumonia, and those who weighed less than 5 kg because of blood-drawing maximums. Biomarkers were measured only in children with focal findings on chest x-ray in the ED. The primary outcome was disease severity: mild (defined as discharged home), moderate (defined as hospitalized, but not severe) and severe (defined as having an ICU length of stay of greater than 48 hours, chest drainage, severe sepsis, noninvasive positive pressure ventilation, intubation, vasoactive infusions, or death).

Over a period of 4.5 years, the researchers enrolled 1,142 patients. Of these, 478 had focal findings on chest x-ray and blood obtained. The median age of these 478 children was 4.4 years, 52% were male, and 82% had all three biomarkers performed. Specifically, 456 had CRP and PCT performed, while 358 had proADM performed. "Not every child had every marker performed due to challenges in obtaining sufficient blood for all three biomarkers in some children," Dr. Florin explained.

Preliminary data that Dr. Florin presented at PAS found that the median CRP, PCT, and proADM did not differ by gender, race, ethnicity, or insurance status. "In addition, there were not significant differences in the distribution of disease severity by biomarker performed, with approximately 27% of patients being classified as mild, 66% as moderate, and 7% as severe," he said.

The median CRP was 2.4 ng/mL in those with mild disease, 2.5 ng/mL in those with moderate disease, and 6.25 ng/mL in those with severe disease, with the difference between the two subclasses of nonsevere disease and moderate disease and severe disease reaching statistical significance ($P = .002$). The median PCT was 0.16 ng/mL in those with mild disease, 0.26 ng/mL in those with moderate disease, and 0.49 ng/mL in those with severe disease, with the difference between the two subclasses of nonsevere disease and moderate disease and severe disease reaching statistical significance ($P = .047$).

Meanwhile, the median proADM was 0.53 ng/mL in those with mild disease, 0.59 ng/mL in those with moderate disease, and 0.81 ng/mL in those with severe disease, with the difference between the two subclasses of nonsevere disease and moderate disease and severe disease also reaching statistical significance (P less than .0001).

Conclusions

Dr. Florin concluded saying that he is "cautiously optimistic" about the study results. "As is the case in many biomarker studies, I do not anticipate that any single biomarker will be the magic bullet for predicting disease severity in pediatric CAP," Dr. Florin said. "It will likely be a combination of clinical factors and several biomarkers that will achieve optimal prognostic ability. That said, our results suggest that, similar to adult studies, proADM appears to have the strongest association with severe disease, compared with CRP and PCT. Combinations of biomarkers did not perform better than proADM alone."

The study received funding support from the Gerber Foundation, the National Institute of Allergy and Infectious Diseases, and Cincinnati Children's Hospital Medical Center. Dr. Florin reported having no financial disclosures.

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VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: This review excellently summarizes a pivotal study by Cincinnati Children's Hospital. Proadrenomedullin appears to be the best biomarker found by these researchers to predict disease severity and included a robust number of study subjects screened but a smaller group (478 out of 1,142 enrolled) in their ER over a period of 5 years. A multicenter study is an important next step.

ILLUMINATEOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Elevated eosinophils are seen in the airways of approximately 50% of patients with severe asthma, and are a **direct cause of chronic inflammation**, which can lead to progressive damage in the airways.[1-3]

Patients with eosinophilic asthma (e-asthma) can experience frequent exacerbations requiring oral corticosteroid (OCS) use, emergency visits, or hospitalizations.[3,4,5] Use of OCS may leave patients susceptible to **steroid-associated adverse events and comorbidities**.[6]

Learn more about how testing patients for e-asthma can help inform clinical decision making at illuminatEOS.com

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AstraZeneca

Simple tool improves inpatient influenza vaccination

BY DOUG BRUNK
MDedge News

TORONTO – Implementation of a simple screening tool improved the influenza vaccination status of hospitalized children, results from a single-center study showed.

"When we looked at the immunization status of children in New York City, we found that one of the vaccines most commonly missed was influenza vaccine, especially from 2011 through 2014," one of the study authors, Anmol Goyal, MD, of SUNY Downstate Medical Center, Brooklyn, N.Y., said in an interview at the Pediatric Academic Societies meeting.

"Given this year's epidemic of influenza and the increasing deaths, we decided to look back on interventions we had done in the past to see if any can be reimplemented to help improve the vaccination status for these children," he said. "The national goal is 80%, but if we look at the recent trend, even though we have been able to improve vaccination status, it is still below the national goal." For example, he said, according to New York Department of Health data, the 2012-2013 influenza vaccination rates in New York City were 65% among children 6 months to 5 years old, 47% among those 5-8 years old, and 31% among those 9-18 years old, which were well below the national goal.

Doug Brunk/MDedge News

Dr. Anmol Goyal said "one of the vaccines most commonly missed was influenza vaccine."

In an effort to improve influenza vaccine access, lead author Stephan Kohlhoff, MD, a pediatric infectious disease specialist at the medical center, and his associates, implemented a simple vaccine screening tool to use in the inpatient setting as an opportunity to improve vaccination rates among children in New York City. It consisted of nursing staff assessing the patient's influenza immunization status on admission and conducting source verification using the citywide immunization registry, or with vaccine cards brought by parents or guardians during admission. Influenza vaccine was administered as a standing order before discharge, unless refused by the parents or guardians. The study population comprised 602 patients between the ages of 6 months and 21 years who were admitted to the inpatient unit during 2 months of the influenza season (November and December) from 2011 to 2013.

Dr. Goyal, a second-year pediatric resident at the medical center, reported that the influenza vaccination status on admission was positive in only 31% of children in 2011, 30% in 2012, and 34% in 2013. The vaccine screening tool was implemented in 64% of admitted children in 2012 and 70% in 2013. Following implementation, the researchers observed a 5% increase in immunization rates in 2012 and an 11% increase in 2013, with an overall increase of 8% over 2 years (*P* less than .001). He was quick to point out that the influenza rate could have been improved by an additional 22% had 77% of patients not refused vaccination.

The researchers reported having no financial disclosures.

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Respiratory allergies linked to autism spectrum disorder

BY MADHU RAJARAMAN
MDedge News

The prevalence of respiratory and other allergies is greater in U.S. children with autism spectrum disorder (ASD) than in U.S. children without the disorder, according to findings published in JAMA Network Open.

An analysis of data from the National Health Interview Survey found that the weighted prevalence of respiratory, skin, and food allergies was, 18.73%, 16.81%, and11.25%, respectively, in children with ASD, compared with 12.08%, 9.84%, and 4.25%, respectively, in children without ASD (*P* less than .001).

Survey data were collected between 1997 and 2016, and included patients aged 3-17 years. Allergic conditions were defined by the respondent, usually a parent, answering in the affirmative that the child had any kind of respiratory, food, digestive, or skin allergy in the past 12 months. ASD was defined based on an affirmative response to a question asking whether the child received an ASD diagnosis from a health professional, wrote Guifeng Xu, MD, of the department of epidemiology at the University of Iowa, Iowa City, and her coauthors.

Of the 199,520 children included in the study, 24,555 had respiratory allergy, 8,734 had food allergy, and 19,399 had skin allergy. An ASD diagnosis was reported in 1,868 children. The weighted prevalence was 12.15% for respiratory allergy (95% confidence interval, 11.92%-12.38%), 4.31% for food allergy (95% CI, 4.20%-4.43%), and 9.91% for skin allergy (95% CI, 9.72%-10.10%), the authors said.

Overall, children with ASD were more likely to have a respiratory, food or skin allergy (*P* less than .001).

Respiratory allergy and skin allergy also were significantly associated with ASD, but to a lesser degree, with an odds ratio of 1.53 (95% CI, 1.32-1.78; *P* less than .001) for respiratory allergy and 1.80 (95% CI, 1.55-2.09; *P* less than .001) for skin allergy, Dr. Xu and her colleagues reported.

The findings suggest a "possible presence of shared mechanisms (e.g., immunologic dysfunction) among these allergic conditions in relation to ASD," though the underlying mechanisms still need to be identified, the authors wrote.

"Large prospective cohort studies starting from birth or early life are needed to confirm our findings," the authors concluded.

No conflicts of interest were reported.

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SOURCE: Xu G et al. JAMA Network Open. 2018 Jun 8. doi: 10.1001/jamanetworkopen.2018.0279.

FDA approves epinephrine autoinjector for infants

BY IAN LACY
MDedge News

The AUVI-Q 0.1 mg, an epinephrine autoinjector (EAI) for infants and toddlers weighing 16.5-33 pounds, was available by prescription beginning May 1, 2018, according to a press release from Kaléo, a privately-held pharmaceutical company.

"Anaphylactic reactions can be frightening and serious, and when experienced by the very young, some of whom can't communicate about what's happening, these episodes can be particularly alarming,"

It features a shorter, retractable needle and a lower dose of epinephrine than other EAIs have, which makes it ideal for young children.

Vivian Hernandez-Trujillo, MD, a pediatric allergist and fellow of the American Academy of Allergy, Asthma, and Immunology, said in a statement. "Now, caregivers can have the AUVI-Q 0.1 mg in hand to respond to an allergic emergency and safely administer epinephrine to infants and toddlers."

The device was granted Priority Review by the FDA because of its potential to significantly improve treatment of a serious condition and was approved Nov. 20, 2017. The injection is indicated to treat life-threatening allergic reactions, including anaphylaxis, in infants and toddlers. It features a shorter, retractable needle and a lower dose of epinephrine than other EAIs have, which makes it ideal for young children. This EAI also features a voice instruction system that provides caregivers step-by-step instructions on how to administer treatment. The epinephrine autoinjector also comes with two autoinjectors, plus an additional trainer for patients and caregivers to practice so they are prepared in an emergency situation.

The approval comes at a time when a higher percentage of children are being admitted to the hospital for food-related anaphylaxis: a 130% increase among children aged 0-4 years and a 196% increase in children aged 5-17 years.

The epinephrine autoinjector has been available for $0 out of pocket for commercially insured patients using the AUVI-Q AffordAbility Program and Direct Delivery Service since May 1, 2018.

ilacy@mdedge.com

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: AUVI-Q is a sleek device and is now supplied in 0.1-mg, 0.15-mg, and 0.3-mg dosing sizes. This is extremely exciting for treating older infants and toddlers.

Simple bedside tool effectively detected sepsis in the ED

BY DOUG BRUNK
MDedge News

SAN DIEGO – The product of pulse pressure and heart rate was more accurate in identifying the presence of culture-positive sepsis, compared with the quick Sequential Organ Failure Assessment prompt, a small, single-center study showed.

"We know a lot about the pathophysiology of sepsis, but we don't have great ways of identifying septic patients at an early stage," lead study author David Lynch, MD, said in an interview at an international conference of the American Thoracic Society.

He noted that screening tools such as the quick Sequential Organ Failure Assessment and Systemic Inflammatory Response Syndrome criteria have a sensitivity of about 70% in detecting sepsis. "Over the last 10-15

years we've been able to find ways of improving outcomes in patients whom we confirm are septic with early antibiotics and fluids," said Dr. Lynch, a second-year resident in the division of pulmonary and critical care medicine within the department of medicine at the University of North Carolina at Chapel Hill. "We know that in sepsis systemic vascular resistance is decreased and cardiac output is increased. We tried to come up with a way of estimating cardiac output at the bedside by multiplying heart rate with pulse pressure, with the pulse pressure being the surrogate for stroke volume, which you can measure easily."

In a cross-sectional, observational study, Dr. Lynch, senior author Thomas Bice, MD, and their associates reviewed the records of 116 patients who were admitted directly to the University of North Carolina's medical ICU (MICU) from the UNC ED between Jan. 5, 2016, and June 30, 2017. The primary outcome of interest was culture-positive sepsis, and the primary exposure was the product of pulse pressure and heart rate. Patients were determined to be positive for sepsis if an infection was suspected (such as if blood cultures were drawn and antibiotics were started), the admitting physician suspected sepsis, and cultures were subsequently positive.

The average age of all patients was 53 years, 51% were female, the mortality rate was 12%, and the median length of stay was 4 days. A total of 25 of the 116 patients (22%) were positive for sepsis. The researchers observed that the pulse pressure multiplied by the heart rate was significantly higher in the culture-positive sepsis group, compared with controls (6,710 vs. 3,741, respectively; *P* less than .001).

Doug Brunk/MDedge News

"We were surprised by how high the sensitivity was. The question is, will this translate to a larger cohort?" said Dr. David Lynch.

Dr. Lynch and his associates found that, as a continuous variable, pulse pressure multiplied by the heart rate accurately classified 90% of sepsis cases (area under the receiver operator curve, 0.96; *P* less than .001). When use of 5,000 as a cutoff, pulse pressure multiplied by the heart rate had a sensitivity of 100% and a specificity of 89% in detecting culture-positive sepsis. "We were surprised by how high the sensitivity was," Dr. Lynch said. "The question is, will this translate to a larger cohort? And, would this be transferable to all patients in the ED, as opposed to the sicker patients who are going to the MICU?"

He and his associates plan to confirm the study's results in a broader population of patients. "We don't yet understand at what point in time this would be most applicable," he added. "We looked at the first set of vitals when they came into the ED. We'd like to know if that applies to the second, third, and fourth set of vitals, and whether it would be most useful to have an average of those."

The study was supported in part by a grant from the National Institutes of Health. Dr. Lynch reported having no financial disclosures.

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Sepsis-associated coagulopathy ups mortality risk

BY ANDREW D. BOWSER
MDedge News

Patients with sepsis-associated coagulopathy appear to be at heightened risk of death, according to results of a large retrospective cohort study.

The risk of death in the study increased with the severity of the sepsis-associated coagulopathy, which was defined using international normalized ratio (INR) and platelet counts.

Those findings suggest that the severity of coagulation abnormalities might be used to quantify mortality risk, according to investigator Patrick G. Lyons, MD, of the division of pulmonary and critical care medicine, Washington University, St. Louis, and his coinvestigators.

"Future trials of sepsis therapies targeting the coagulation cascade should take into account the presence or absence of sepsis-associated coagulopathy, as well as the severity of sepsis-associated coagulopathy, when formulating potential trial designs," the investigators wrote in the journal Critical Care Medicine.

Their retrospective cohort study included 6,148 consecutive patients with sepsis or septic shock hospitalized at a 1,300-bed urban academic medical center between 2010 and 2015. Of that group, 26% had sepsis-associated coagulopathy, defined as having both an INR of 1.2 or higher and a platelet count less than 150,000/mcL. Sepsis-associated coagulopathy was classified as mild for 4%, moderate for 16%, and severe for 6% of the cohort.

Hospital mortality was 25.4% for patients with no sepsis-associated coagulopathy, the research team found, increasing progressively from 27.0% for mild, 40.7% for moderate, and 56.1% for patients in the most severe category of sepsis-associated coagulopathy (*P* less than .001).

Hospital and ICU days also increased progressively according to the severity of coagulopathy, they wrote.

Both presence and severity of sepsis-associated coagulopathy remained independently associated with hospital mortality even after adjustments were made for patient characteristics, hospitalization variables, and interactions between sepsis-associated coagulopathy and cancer, investigators said. Odds ratios ranged from 1.33 to 2.14 for presence of sepsis-associated coagulopathy, and from 1.18 to 1.51 for severity, they reported in the journal.

"This could have important implications for comparing the outcomes of patients with sepsis from different hospitals, especially with increasing requirements for public reporting of such data through systems such as the Severe Sepsis/Septic Shock Early Management Bundle-1 and New York State's Rory's Regulations," the investigators wrote.

Reported disclosures for the study included institutional funding from Asahi Kasei Pharma America by one coauthor, and support from Barnes-Jewish Hospital Foundation by another. No other potential conflicts of interest were reported.

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SOURCE: Lyons PG et al. Crit Care Med. 2018 May;46(5):736-42.

VIEW ON THE NEWS

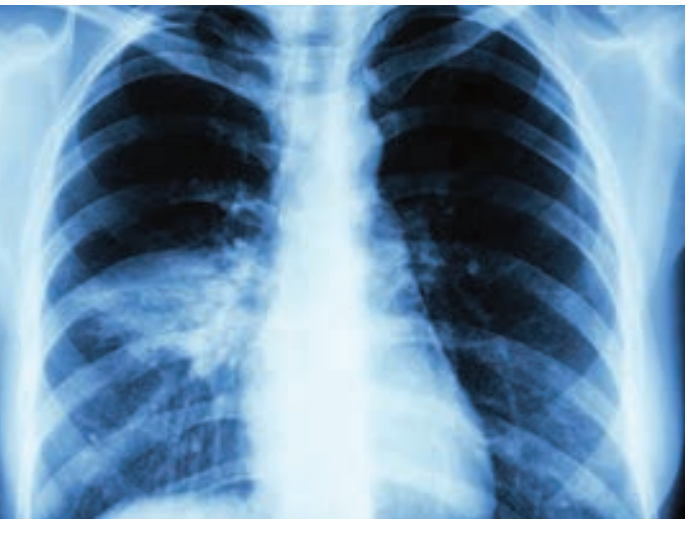
Jennifer Cox, MD, FCCP, comments: Lyons et al. used predefined cutoff values for INR and platelets to define the presence and graded severity (mild, moderate, and severe) of sepsis associated coagulopathy. In this study, we have further evidence that sepsis-associated coagulopathy has implications on mortality. As mentioned in the article, human activated protein C was removed from the market after subsequent trials found no mortality benefit. Given it's mechanism of action and the low volume of patients with moderate to severe sepsis-associated coagulopathy in the trial, a potential benefit may have been missed. Here is where this retrospective cohort study gives me hope. Platelet count and INR are routine labs that are ordered on virtually every patient coming to the ICU. If the increase in mortality seen using these common variables to predict and stratify sepsis-associated coagulopathy hold up with further research, this could prove to be a simple yet effective tool to identify the cohort of patients that should be studied in future trials of new/novel sepsis drugs aimed at the coagulation cascade. Maybe it could re-open the debate on human activated protein C.

In-hospital mortality predictors eyed in pneumonia patients

BY DOUG BRUNK
MDedge News

SAN DIEGO – About one in four intubated or mechanically ventilated (MV) patients with gram-negative pneumonia die during hospitalization, results from a large retrospective cohort study found.

In a poster abstract presented at an international conference of the American Thoracic Society, researchers led by Thomas P. Lodise Jr., PharmD, noted that ventilator-associated pneumonia is one of the most common hospital-acquired infections in intensive care units and affected an estimated 9%-27% of all intubated patients.



STOCKDEVIL/THINKSTOCK

In an effort to describe mortality rates and associated risk factors for intubated and MV patients diagnosed with gram-negative pneumonia, Dr. Lodise of the Albany (N.Y.) College of Pharmacy and Health Sciences and his associates conducted a retrospective cohort study of data from the Healthcare Cost and Utilization Project (HCUP) National Readmission Database (NRD). HCUP is the largest source of hospital care data in the United States, accounting for 49.3% of the total U.S. resident population and 49.1% of U.S. hospitalizations. The researchers included patients at least 18 years of age who were hospitalized with a primary or secondary diagnosis of gram-negative pneumonia between Feb. 1, 2013, and Nov. 30, 2013. They excluded index hospitalizations with a primary or secondary diagnosis of viral pneumonia, fungal pneumonia, atypical organisms, gram-positive bacterial pneumonia, or pneumonia occurring secondary to an infectious disease. They examined mortality rates descriptively and modeled them via adjusted multivariate logistic regression to evaluate the impact of baseline characteristics and comorbidities.

A total of 32,683 patients met all study criteria. Of these, 2,323 (7.1%) had a primary diagnosis and 30,360 (92.9%) had a secondary diagnosis for gram-negative pneumonia. Their mean age was 64 years, and 61.1% were male. In all, 7,928 patients (24.3%) died during hospitalization. Multivariate analysis revealed that patients with concomitant sepsis had the highest risk of mortality (odds ratio, 2.60), followed by patients aged 65 years and older (OR, 1.88) and those with any prior hospitalization within 30 days (OR, 1.34). Comorbidities upon admission with highest risk of mortality included cancer (OR, 2.45), liver disease (OR, 1.91), AIDS/HIV (OR, 1.59), renal disease (OR, 1.33), and congestive heart failure (OR, 1.15). Diabetes was found to have a decreased risk of mortality, with an OR of 0.80. "However, a majority of patients with diabetes had no complications; thus, these patients may be representative of a less severe patient population," the authors noted.

They acknowledged certain limitations of the study, including the potential for coding errors. They also pointed out the HCUP NRD does not contain treatment-specific information, drugs administered or treatment patterns during hospitalization, the number of days patients spent in the ICU, or the number of days on ventilation. Bayer Healthcare Pharmaceuticals funded the study. Dr. Lodise reported having no financial disclosures.

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NOW APPROVED
TO REDUCE COPD EXACERBATIONS

See the following pages for
IMPACT *TRIAL*
Infor**M**ing the
PAthway of
COPD **T**reatment

For appropriate patients with COPD

LESS TO TAKE. MORE TO TAKE IN.

TRELEGY—the only once-daily triple therapy (ICS/LABA/LAMA) for COPD delivered in a single inhaler

ICS=inhaled corticosteroid; LABA=long-acting beta$_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist.

INDICATION

TRELEGY is for maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (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, umeclidinium, vilanterol, 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.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Patient Information, for TRELEGY following this ad.

gsk | INNOVIVA

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

IMPACT TRIAL

INFORMING THE PATHWAY OF COPD TREATMENT

A landmark study for patients with a history of COPD exacerbations

10,000+ PATIENTS

Symptomatic patients with at least 1 COPD exacerbation in the last year while on maintenance medication[1,2]*

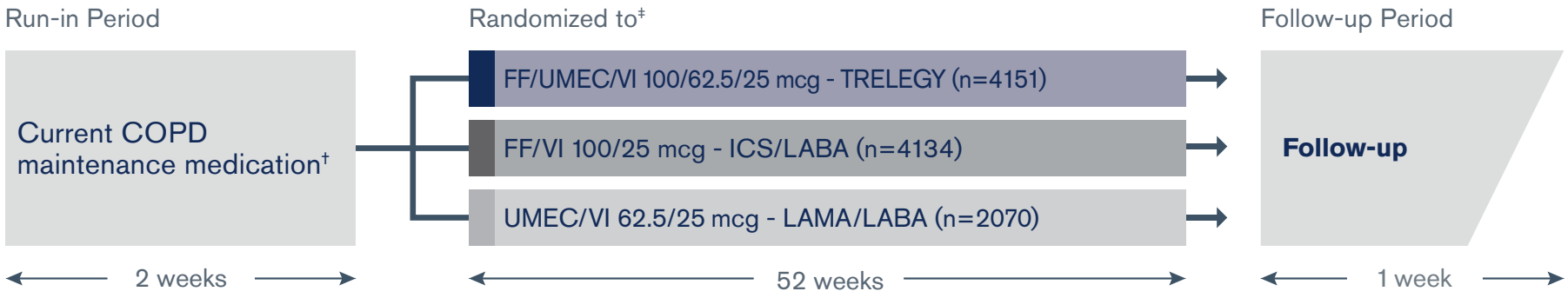
52-WEEK STUDY

A randomized, double-blind, 3-arm, parallel group; primary endpoint measured was the annual rate of moderate to severe exacerbations

1ST AND ONLY

First and only trial to study the efficacy and safety of triple therapy vs an ICS/LABA and vs a LAMA/LABA in an exacerbating COPD population

DESIGNED TO REFLECT CLINICAL PRACTICE



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

*Eligible patients 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. At screening, patients (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.

†Current maintenance medications included ICS + LABA + LAMA, ICS + LABA, LAMA + LABA, LAMA, and other.

‡Each delivered once daily via the ELLIPTA inhaler.

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting $beta_2$-adrenergic agonist; LAMA=long-acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol.

IMPORTANT SAFETY INFORMATION (cont'd)

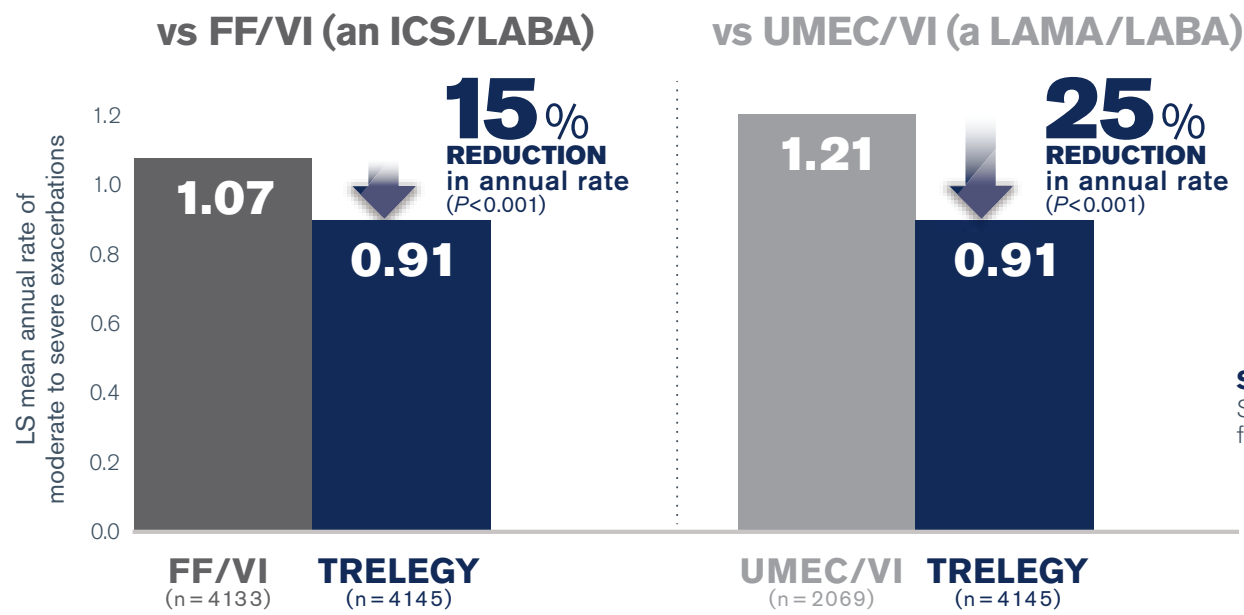
WARNINGS AND PRECAUTIONS (cont'd)

- 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 inhaled corticosteroids, like fluticasone furoate.

Please see additional Important Safety Information for TRELEGY on the following pages.
Please see Brief Summary of Prescribing Information, including Patient Information, for TRELEGY following this ad.

In the landmark IMPACT TRIAL, TRELEGY was proven the most effective treatment for reducing moderate to severe exacerbations vs FF/VI (an ICS/LABA) and vs UMEC/VI (a LAMA/LABA)

PRIMARY ENDPOINT: ANNUAL RATE OF MODERATE TO SEVERE EXACERBATIONS



STUDY DESCRIPTION
See previous page for description

UMEC/VI is not approved for the reduction of COPD exacerbations.

LS=least squares.

Prescribe TRELEGY—the only once-daily triple therapy (ICS/LABA/LAMA) for COPD delivered in a single inhaler

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- 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 TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased 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.

Learn more about the *IMPACT TRIAL* at TrelegyMD.com

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

TRELEGY does not replace a rescue inhaler.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- 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.
- 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 prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of inhaled corticosteroids or inhaled anticholinergics; therefore, monitoring is warranted.
- 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 umeclidinium + 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 on the previous pages.
Please see Brief Summary of Prescribing Information, including Patient Information, following this ad.

References: 1. Data on file, GSK. **2.** Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple vs dual therapy in patients with COPD [published online April 18, 2018.]. *N Engl J Med*. doi:10.1056/NEJMoa1713901.

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

Printed in USA. 1004815R0 May 2018

TRELEGY ELLIPTA
(fluticasone furoate, umeclidinium, and vilanterol 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 ELLIPTA 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 ELLIPTA in patients with asthma have not been established. TRELEGY ELLIPTA 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 ELLIPTA (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 ELLIPTA, 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.

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

Continued on next page

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 long-term 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 ELLIPTA (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 ELLIPTA, 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. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, and/or cataracts.

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 ELLIPTA 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 ELLIPTA 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 ELLIPTA, 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 ELLIPTA (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 long-term 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 ELLIPTA. 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.

Ocular Effects

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

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

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

Could Right to Try law undermine drug safety?

BY GREGORY TWACHTMAN
MDedge News

The Food and Drug Administration is generally achieving the balance between ensuring safety and providing access to investigational drugs through compassionate-use programs, according to results from a new analysis that found that most of these drugs are available within 6 months of an application to the FDA.

But that balance may be undermined by the recently enacted Right to Try Act, Jeremy Puthumana, of Yale University, New Haven, Conn., and his colleagues reported in an article published on JAMA Network Open. They said the new law encourages sponsors to make investigational drugs available earlier in the clinical development period, potentially jeopardizing safety.

"These findings suggest the FDA and the pharmaceutical industry have established a balance between investigational new drug access and protection of patients from therapies without established safety, which may be compromised by policy makers seeking to speed access to investigational medicines through the Right to Try Act by removing the requirements for FDA oversight and approval of expanded access requests," the researchers wrote.

The cross-sectional study examined all expanded-access programs registered with ClinicalTrials.gov through Aug. 1, 2017. Of 92 expanded-access programs for investigational drugs, 69.6% were initiated within 6 months following (43.5%) or preceding (26.1%) submission of a new drug application. Ninety of the 92 drugs ultimately went on to receive FDA approval.

Of the most common uses of the 92 drugs registered in expanded-access programs between September 1996 and June 2017, half were used for the treatment of cancer; 16 drugs were used to treat metabolic, endocrine, and genetic diseases; and 14 drugs were used for the treatment of infectious diseases. But there were no significant differences in the timing of program initiation by therapeutic characteristics, the researchers found.

President Trump signed the Right To Try Act of 2017 (S. 204) into law on May 30, 2018, despite opposition from physician and patient groups who expressed concerns that the law will remove FDA safeguards.

The study was funded by a grant from the National Institutes of Health. The researchers reported research support from the Laura and John Arnold Foundation, Johnson and Johnson, Medtronic, the Blue Cross-Blue Shield Association, the FDA, and other federal agencies.

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Reducing liability by improving doc-nurse teams

BY ALICIA GALLEGOS
MDedge News

Positive relationships between physicians and nurses not only make for a smoother work environment, they also may reduce medical errors and lower the risk of lawsuits.

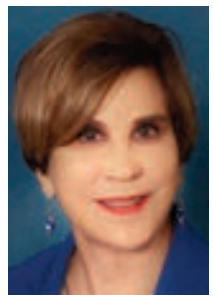
A recent study of closed claims by national medical malpractice insurer The Doctors Company found that poor physician oversight is a key contributor to lawsuits against nurses. Investigators analyzed 67 nurse practitioner (NP) claims from January 2011 to December 2016 and compared them with 1,358 claims against primary care physicians during the same time period.

Diagnostic and medication errors were the most common allegations against NPs, the study found, a trend that matched the most frequent allegations against primary care (internal medicine and family medicine) doctors. Top administrative factors that prompted lawsuits against nurses included inadequate physician supervision, failure to adhere to scope of practice, and absence of or deviation from written protocols.

The findings illustrate the importance of effective collaboration between physicians and NPs, said Darrell Ranum, vice president for patient safety and risk management for The Doctors Company. Below, legal experts share six ways to strengthen the physician-nurse relationship and at the same time, reduce liability:

1. Foster open dialogue. Cultivating a comfortable environment where nurses and physicians feel at ease sharing concerns and problems is a key step, says Louise B. Andrew, MD, JD, a physician and attorney who specializes in litigation stress management. A common scenario is a nurse who notices an abnormal vital sign but fails to mention it to the supervising physician because they feel they can handle it themselves or because they believe the doctor is too busy or too tired to be bothered, she said. The patient's condition then worsens, resulting in a poor outcome that could have been avoided with better communication among providers. Delayed/wrong diagnosis accounted for 41% of claims against primary care physicians and 48% of claims against NPs in The Doctors Company study.


DR. ANDREW


MS. BALESTRA

"Nurses must not be afraid to ask doctors why they are doing something, and to inquire further if they see something they don't understand," Dr. Andrew said in an interview. Doctors, on the other hand, have an obligation, no matter how stressed or hurried they may be, not to send signals – bodily or otherwise – that they are not to be approached. That is a recipe for disaster."

Set the tone early by exemplifying positive and clear communication, practicing good listening, and remaining empathetic, yet firm when making your needs known, Dr. Andrew advised.

2. Stick to the scope. When hiring an NP, make sure their scope of practice is clearly understood by all parties and respect their limitations, said Melanie L. Balestra, a Newport Beach, Calif., attorney and nurse practitioner who represents health providers.

Start by knowing your state's scope of practice law for nurse practitioners. In 23 states and the District of Columbia, NPs have full authority to practice independently and can evaluate, diagnose, and manage treatment. In 15 states, NPs have reduced practice authority that requires a regulated collaboration agreement with a physician. In 12 states, NPs have restricted practice authority that requires supervision, delegation, or team management by a doctor.

Nurses practitioners must refrain from overstepping their authority, but physicians also must be careful not to ask too much of their NPs, experts stress. Ms. Balestra notes there is frequent confusion among doctors and NPs over how and whether scope of practice can be expanded as needed.

"This happens all the time," Ms. Balestra said. "I get at least two questions on this every week [from nurses] asking, 'Can I do this? Can I do that?' "

The answer depends on the circumstances, the nurse's training, and the type of practice being broadened, Ms. Balestra said. For example, an NP in cardiology care may be allowed to perform more procedures in that field after internal training, but an NP who is trained in the care of adults can see pediatric patients only by going back to school.

"Know who you're hiring, where their expertise lies, and where they feel comfortable," she emphasized.

3. Preplan reviews. Early in the doctor-NP relationship, discuss and decide what type of medical cases warrant physician review, Mr. Ranum said. This includes agreeing on the type of patient conditions that will require a physician review and determining the types and percentage of medical records the doctor will evaluate, he said.

"The numbers should be higher at the beginning of the relationship until the physician gains an understanding of the NP's experience and competence," Mr. Ranum said. "Setting expectations will open the door to more frequent and more effective communication."

NPs, meanwhile, should feel confident in requesting the physician's assistance when a patient's presentation is complex or a patient has returned with the same complaints, he added.

4. Convene regularly. Schedule regular meetings to catch up and discuss patient cases – not just when something goes awry, said Ms. Balestra. During weekly or monthly meetings, physicians, NPs, and oth-

Continued on following page

Continued from previous page

er team members can converse in a more relaxed atmosphere and share any concerns or ideas for improvements.

"Have a meeting, whether by phone or in person, just to see how things are going," she said. "That way, the NP may be able to take some things off the plate for the physician and the physician can see how [he or she] can assist the NP."

"It is often helpful to debrief on patients who were seen during that day and who represent complex conditions," he said. "Physicians may see opportunities to improve care following the NP's assessment and diagnosis."

5. Consider noncompliant policy. Create a noncompliant patient policy and work together to address uncooperative patients. Noncompliant patients are a top lawsuit risk, Ms. Balestra said. A noncompliant patient for instance, may provide conflicting information to different health professionals or attempt to blame providers for adverse events, she said.

"Your noncompliant patient is your easiest patient for a lawsuit because they're not following [instructions] and then something happens, and they say, 'It's your fault, you didn't treat me right.'"

Physician and NPs should be on the same page about noncompliant patients, including taking time to discuss when and how to terminate them from the practice if necessary, she said. Consistent documentation about patients by both physician and NPs is also critical, experts emphasize. Insufficient or lack of documentation led to patient injuries in 17% of cases against primary care doctors and in 19% of cases against NPs in The Doctors Company study.

6. Keep patients out of it. When disagreements or grievances occur, discuss the problem in private and ensure all staff members do the same, Dr. Andrew said. Refrain from letting anger or annoyance with another team member carry into patient care or worse, trigger a negative comment about a staff member in front of a patient, she said.

"All it takes is for something to go wrong and a patient or family who has heard such sentiments is tuned into the fact there may be some culpability," she said. "This is probably a key factor in many a claimant's decision to seek redress for a bad outcome."

Instead, address problems or differences as soon as possible and work toward a resolution. It may help to create a conflict resolution policy that outlines behavioral expectations from all team members.

"We have to put our egos aside," Ms. Balestra said. "The ultimate goal is the best care of the patient."

chestphysiciannews@chestnet.org

FROM THE EVP/CEO

CHEST heading into a very active fiscal year

BY STEPHEN J. WELCH,
CHEST Executive Vice President & CEO

As we wrap up CHEST's fiscal year 2017-18 (our fiscal year runs July 1 – June 30), it has been an incredibly positive and productive year, on all fronts. We have educated more learners than ever before, expanded our educational offerings, increased our collaboration with other organizations, grown our CHEST Foundation activities, and are in excellent financial shape to continue our commitment to clinical chest medicine education.


MR. WELCH

As we prepare for fiscal year 2018-19, I want to highlight some of the key programs, events, and projects we will be undertaking that will support our strategic plan (http://www.chestnet.org/About/Overview/Strategic-Plan) and achieve our mission to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research.

Our organization goals are primarily focused on (but are not limited to) the following broad achievements:

a Increasing the number of learners that CHEST engages (and increasing their engagement with our content) and assessing the results of our educational interactions

b. Keeping our journal *CHEST*® among the top Pulmonary, Critical Care, and Sleep peer reviewed journals in the world

c. Expanding domestic and global access to CHEST guidelines and other relevant clinical content

d. Continuing to offer a positive and inclusive culture and work environment at CHEST, for our volunteers, world-class faculty, members, and staff

e. Meeting or exceeding our budget, reserve policy, and grant funding targets to ensure delivery of our mission-based educational efforts and programs

Because our mission as a 501(c)3 not-for-profit is education, I'll start with those key programs that are driving our budget for FY2018-19 and will also cover publishing and membership.

Education – Clinical

- Increased global activity due to global partnerships with several key international educational providers
  - Holding April 2019 CHEST World Congress in Bangkok
  - Planning June 2019 Board Review conference in Athens, Greece
  - 21 total international courses planned
- Increased Live Learning courses, simulation, and hands-on skills training
  - 21 courses planned (including 3 new courses)
  - Holding two fellows courses at CHEST HQ (up to 80 fellows)
  - Annual Meeting includes 11 postgraduate programs and 24 simulation courses (including more cadaver courses)
    - Includes more fellows courses (up to 240 fellows)
- Board Courses include two half-day simulation courses; more sponsorship/exhibits, games, and virtual patient tours (VPTs)
- Continuing to build Board Review on-demand and e-learning content packages for those who cannot attend live events
- Launching inaugural e-Learning program with Elsevier

Education – Patient

- Developing multiple CHEST Foundation disease awareness campaigns and patient education resources
  - New patient education guides
  - Increased visual content (infographics, graphically based materials)
  - Increased use of multimedia and video content
- Increased funding for clinical research grants, community service programs and lung health events, and fund raising through cause marketing (ie, Feldman Family Poker Night, NYC events, and other local fund raising events)
- Expanding awareness of and access to our patient education materials
  - Institutions, large group practices
  - International reach
  - Digital distribution via social media and online campaigns

Education – Industry

- Projecting seven new live clinical immersion courses
- Two new proposed PREP courses with CTS
- Expansion of educational games, VPTs, and e-learning
- Expanded CHEST Analytics product lines
  - View Points (3 focus groups, 4-5 KOL panels, 4 pulse surveys)
  - Deep Dives (3 advanced analytics projects, 5 premium research projects, 2 ethnography studies, and 4-6 Clinical Perspectives)
  - Data Lab (looking to launch beta partner)
  - Booth IQ (increasing capacity for booth flow and booth intel reports)

Publications, Guidelines and Digital Content

- *CHEST*® Journal
  - Elsevier partnership remains strong; leveraging key data and Elsevier offerings, will be announcing the next Editor in Chief
- CHEST Physician
  - New content and delivery mechanisms
    - Supplements
    - Electronic features
- CHEST SEEK
  - Publish Volume 28 (Critical Care)
  - Continue development of SEEK online library
- Guidelines
  - **Completions:** Antithrombotic therapy, cough, ILD diagnosis, hypersensitivity pneumonitis, lung cancer, and PAH
  - **Updates:** Antithrombotic therapy, lung cancer, cough, neuromuscular weakness, EBUS needle sampling, and blood transfusions in critical care setting (doing more in critical care)
  - Piloting use of DoctorEvidence methodology services and platform for "living guidelines"

Membership

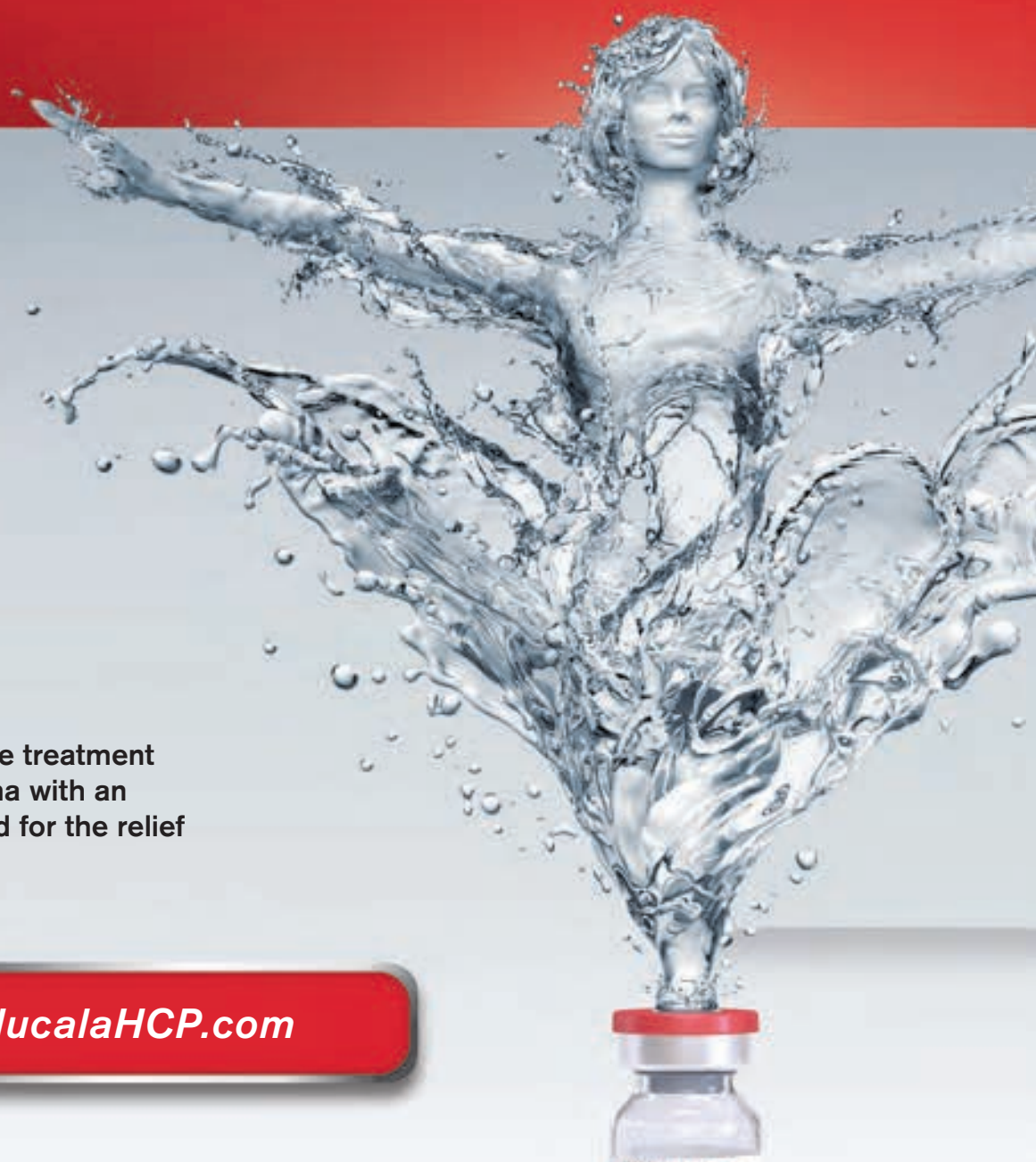
- Focusing on adding value to CHEST membership for key segments
- Bundling e-learning packages with membership
- Exploring international group/society memberships and group practice/institutional memberships
- Working to attract advanced practice providers
- Performing member market research, including member satisfaction, net promoter scores, and other key metrics

Supporting Divisions (Finance, Marketing, IT, Capital Expenses)

- Have more visibility (booth presence) at more meetings (AACN, AARC (new), ALAT, APSR, ATS, CTS, ERS, SCCM, and more)
- Develop and execute comprehensive marketing and branding strategies for all business units
  - Clinical Education (CHEST annual meeting, Board Reviews, all int'l meetings and live learning, simulation)
  - Industry Education (PREP, CHEST Analytics)
  - Patient Education
  - Foundation Fundraising
  - Publishing and Content Strategy
  - Membership
- Support new IT platforms and bolster security (HR, Finance, Board Effect, Tableau, CHEST Analytics, LMS, CMS, NetForum AMS), as well as marketing and social interaction tools (HubSpot)
- Maintain Capital Budget for building, infrastructure, technology, etc

All in all, CHEST has a very active fiscal year planned, with a number of new educational programs and e-learning opportunities showcasing CHEST's unique brand of innovative clinical education. We look forward to connecting with you and impacting health-care delivery and patient outcomes.

It is an honor and a privilege to be able to lead this organization, and all of this news is directly attributable to our dedicated volunteer leadership, faculty, content expertise, staff, and valuable time that you all contribute to make this organization great. Thank you for your ongoing support of CHEST.



NUCALA—Prescribe with confidence

The first anti-interleukin 5 (IL-5) for severe eosinophilic asthma

NUCALA is indicated for the add-on maintenance treatment of patients 12 years and older with severe asthma with an eosinophilic phenotype. NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

DiscoverNucalaHCP.com

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred with NUCALA. These reactions generally occur within hours of administration but can have a delayed onset (ie, days). If a hypersensitivity reaction occurs, discontinue NUCALA.

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred with NUCALA compared to none with placebo. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until infection resolves.

ADVERSE REACTIONS

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

*As of January 2018, more than 20,000 patients have received NUCALA**

*December 2015 to January 2018 data sourced from IQVIA and GSK. Claims data based on total number of unique patients who had at least 1 claim for NUCALA in the United States. Not all patients remain on therapy. Individual results may vary.[1]

In patients with blood eosinophil levels ≥150 cells/µL,

NUCALA provided a strong and consistent reduction in exacerbations[2,3†]

MENSA

53%

Reduction in exacerbation frequency at Week 32
(*P*<0.001)[2]

MUSCA

58%

Reduction in exacerbation frequency at Week 24
(Rate ratio: 0.42; 95% CI: 0.31, 0.56)[3]

Other endpoint; results are descriptive.
CI=confidence interval.

MENSA (Trial 2) Study Description[2]: 32-week study comparing treatment with NUCALA or placebo added to standard of care (SOC) in 576 patients with severe eosinophilic asthma. **Primary Endpoint:** Frequency of exacerbations.† **Results:** Exacerbations/year 0.83 for NUCALA vs 1.74 for placebo.

MUSCA Study Description[3]: 24-week study comparing treatment with NUCALA or placebo added to SOC in 551 patients with severe eosinophilic asthma. **Primary Endpoint:** Mean change from baseline in St George's Respiratory Questionnaire total score at Week 24. **Results:** –15.6 for NUCALA vs –7.9 for placebo; treatment difference of –7.7 (*P*<0.0001). The improvement in both treatment arms was clinically meaningful (defined as a reduction in score of ≥4 points). **Other endpoint:** Included frequency of exacerbations. **Results:** Exacerbations/year 0.51 for NUCALA vs 1.21 for placebo.

†Exacerbations were defined as the worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits; for patients on maintenance oral/systemic corticosteroids, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

SOC=regular treatment with high-dose inhaled corticosteroids and at least 1 other controller with or without oral corticosteroids

The approved dose of NUCALA for severe eosinophilic asthma is 100 mg administered every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for NUCALA and 5% for placebo. Manifestations included rash, flushing, pruritus, headache, and myalgia. A majority of the systemic reactions were experienced on the day of dosing.

Injection site reactions (eg, pain, erythema, swelling, itching, burning sensation) occurred in subjects treated with NUCALA.

USE IN SPECIFIC POPULATIONS

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. To enroll call 1-877-311-8972 or visit www.mothertobaby.org/asthma.

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

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al; for the MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207. **3.** Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390-400.

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

Printed in USA. 828398R0 March 2018

Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use

The following is a brief summary only and is focused on the indication for maintenance treatment of severe asthma with an eosinophilic phenotype. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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

6.1 Clinical Trials Experience in Severe Asthma

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg SC) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Subjects with Asthma (Trials 2 and 3)

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.

Long-term Safety

Nine hundred ninety-eight subjects received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the asthma trials described above.

6.3 Immunogenicity

In subjects with asthma receiving NUCALA 100 mg, 15/260 (6%) developed anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.4 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. 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 NUCALA or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg SC *(see Data)*.

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

(continued on next page)

8 USE IN SPECIFIC POPULATIONS (cont'd)

8.4 Pediatric Use
The safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the Phase 3 asthma studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.
The safety and efficacy in pediatric patients other than those with asthma have not been established.

8.5 Geriatric Use
Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 46) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE
Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial with eosinophilic disease without evidence of dose-related toxicities.
There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.
Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling.
Hypersensitivity Reactions
Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

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

Opportunistic Infections: Herpes Zoster
Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.

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

Pregnancy Exposure Registry
Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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Mentors creating mentors

BY LAUREN HUGHES
CHEST Marketing Specialist

Upon wrapping up a successful 2018 NetWorks Challenge Giving campaign – supporting travel grants to CHEST 2018 for early career and diverse clinicians, CHEST Foundation staff sat down with one of our champions, Demondes Haynes, MD, FCCP. Our conversation focused heavily on the role of mentorship in the development of early career clinicians and his own experience as both a mentor and mentee.

Dr. Haynes has had several mentors over the course of his career, but one stands out to him in particular: Doug Campbell, MD, FCCP. Dr. Campbell is a pulmonary and critical care physician who was the division chief at the University of Mississippi Medical Center in Jackson.

"When I was finishing my chief residency, the entire pulmonary division imploded. All of the faculty left, except one or two professors, and all those who were going to become fellows here started looking for other places to go. I was actively looking as well… planning to leave my home state, which was not my initial plan. Dr. Campbell came in about that time and promised me that if I gave him some time, we could rebuild the division. He told me if I stayed for my fellowship, I could really help rebuild it. From that day forward, he was my mentor. I stayed for my fellowship under Dr. Campbell.

He delivered on all of those promises. He taught pulmonary medicine extremely well. Not only was he a great clinician, but he built up the faculty – started a telemedicine program for the ICU and brought in a diverse set of faculty who had all trained at other institutions. He really helped build and strengthen the program. I was very happy I chose to stay and learn under his leadership."

Doug Campbell not only had an impact on Dr. Haynes' professional life, but also his personal life.

"When I agreed to stay for my fellowship, he sent a beautiful handwritten note to my mother, thanking her for raising me to be respectful. She was amazed." Dr. Haynes mother passed 10 years ago. The night before the funeral at the visitation, Dr. Campbell brought the card his mother sent back – an exchange that Dr. Haynes never knew took place. "It really meant the world to me, not only had he mentored me in my academic career, but he made those personal touches. Those moments are very special to me."

Dr. Haynes is now mentoring residents and feels it is even more rewarding being a mentor.

"You actually get to invest in others, and when you invest in others, the best comes out in them. Sometimes, in this mentoring role, you're helping people uncover what their qualities are. Sometimes they don't even know what they are capable of until you push them just a little bit. That's been so rewarding. I have been blessed, my mentors have invested so much in me, and I am able to pay it forward and give back."

Dr. Haynes chose to honor Dr. Campbell through giving during the NetWorks Challenge Giving Month. "***The NetWork Challenge is great because part of our mission as an organization is philanthropy. We are an education organization, and, in medicine in general, we should support philanthropy. We talk a lot about empathy for our patients… and giving back is just a small part of that. There is a scripture that says, 'To whom much is given, much is required.' I truly believe that. I believe that it should just be an ingrained part of our calling as physicians.***"

Your generosity funds young clinicians' learning opportunities that will change the future of patient outcomes and lung diseases. Thank you for making these opportunities possible.

Your continued support will advance the next generation of mentees launching their careers (with the proper hands-on training). You can be a Champion for Lung Health and DONATE today through a new gift to the CHEST Foundation by going to chestfoundation.org/donate or calling 224/521-9527.

Again, thank you for all you do to improve patient outcomes. You are the lung health champions who patients and families count on to positively impact lung health.

This month in the journal *CHEST*®

Editor's Picks

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

GIANTS IN CHEST MEDICINE
Arthur S. Slutsky, MD, MASc, BASc
By Dr. Eliot A. Phillipson

ORIGINAL RESEARCH
A Longitudinal Cohort Study of Aspirin Use and Progression of Emphysema-like Lung Characteristics on CT Imaging: The MESA Lung Study
By Dr. C. P. Aaron, et al.

The Effect of Alcohol Consumption on the Risk of ARDS: A Systematic Review and Meta-analysis
By Dr. E. Simou, et al.

The Relationship Between COPD and Frailty: A Systematic Review and Meta-analysis of Observational Studies
By Dr. A. Marengoni, et al.

Explore Ultrasound Corner

BY KRISTIN CROWE
CHEST Marketing and Communications Specialist

The use of ultrasound is often overlooked when it could very well aid in the diagnosis of a critical illness in a shorter amount of time, while eliminating potential risks that come with many of the usually administered tests.

In 2013, Seth Koenig, MD, FCCP, of Hofstra School of Medicine in New Hyde Park, New York, noticed the need to educate providers about the use of ultrasound in the ICU. Dr. Koenig approached Richard Irwin, MD, Master FCCP, and Editor in Chief of the journal *CHEST*®, with an idea for a new section in the journal. So began "Ultrasound Corner," an online, video-based series in the journal that provides readers with real cases where ultrasound has played a large role in diagnostic patient care.

Each month, the journal receives two to four submissions from chest medicine clinicians who want to share their critical care ultrasound patient stories. One to two stories are selected and published monthly with real video images that are explained in the manuscript and in a narration done by Dr. Koenig.

"This creates a section where clinicians worldwide can share their experiences so that others may incorporate different methods of diagnosis into their practice," said Dr. Koenig. "This method of learning challenges the readers to interpret images and integrate the results into a patient management plan."

Dr. Koenig recommends that clinicians who have experienced benefit using ultrasound in critical care situations submit their cases so that viewers can learn from each other. Visit https://mc.manuscriptcentral.com/chest, log in to your account, and click "Start a New Submission" under the "Author" section.

Dr. Koenig encourages the journal readership to explore Ultrasound Corner (https://journal.chestnet.org/ultrasound) every month in CHEST to learn of different courses of diagnosis and treatment being used to strengthen patient diagnostic and management plans in new, evolving ways.

Launching the Moderate to Severe Asthma Center of Excellence

The American College of Chest Physicians (CHEST) announces a new partnership with Medscape focused on supporting physicians in addressing the challenges of diagnosing and treating moderate to severe asthma. The Moderate to Severe Asthma Center of Excellence (https://www.medscape.com/resource/moderate-severe-asthma) will provide news, expert commentary, and insights on challenging cases to physicians specializing in chest medicine, allergy, primary care, pediatrics, and emergency medicine.

Medscape is a leading source of clinical news, health information, and point-of-care tools for physicians and health-care professionals. This new Center of Excellence available on Medscape.com will explore the diagnostic, therapeutic, and prevention strategies associated with moderate to severe asthma, including the latest research and breakthroughs. Topics will include challenges in classifying and diagnosing disease; risks, benefits, and barriers to treatment; and impact on patients' quality of life.

"We look forward to working with Medscape on the Center of Excellence to ensure that all physicians treating patients with asthma have access to the latest information and research on managing this pervasive and challenging disease," said John Studdard, MD, FCCP, President, American College of Chest Physicians.

"The Moderate to Severe Asthma Center of Excellence with CHEST provides a new, accessible channel for information, practical insights, and commentary to the thousands of physicians and health-care professionals who visit Medscape daily," said Jo-Ann Strangis, Senior Vice President, Editorial for Medscape. "We are privileged to be working with CHEST and look forward to the Center of Excellence making a meaningful difference in patient care."

Don't miss Dr. Aaron Holley's video on "Diagnosing Severe Asthma: 'Not as Easy as It Sounds" (https://goo.gl/4v1VHY).

Visit the Moderate to Severe Asthma Center of Excellence: https://goo.gl/6L5u9t.

Family fun in San Antonio during CHEST 2018

Planning on bringing your family with you to CHEST 2018 in San Antonio? Well, we've got you covered on ways to have some family fun when you're not immersed in learning at the convention center. Here are a few activities you can take part in:

San Antonio Missions National Historical Park
There are four San Antonio Missions you can visit: San José, Espada, Concepción, and San Juan. Explore the missions on your own, or join a park ranger or volunteer for a free, 45- to 60- minute guided tour of your chosen mission. While Mission San José is the most popular tour with ranger-led tours between 10:00 AM and 3:00 PM, make sure to stop at the visitor center or information center of the other missions you want to tour to check available tour times.

World's Largest Cowboy Boots
Just outside Saks Fifth Avenue at North Star Mall, you can take a selfie next to the World's Largest Cowboy Boots. These 35-foot tall and 30-foot long boots shouldn't be too hard to spot. Originally the boots were built by Bob "Daddy-O" Wade in Washington, DC, in 1979 and moved to San Antonio just 1 year later.

TODD CARR

The Boots

Cool Off at a Waterpark
While October weather in San Antonio may be slightly cooler than in the summer, it still averages in the mid-80 degrees Fahrenheit, so you'll want to cool off at the pool or a waterpark. Take some downtime with the family and head to one of the several waterparks in the area, including Schlitterbahn, Splashtown San Antonio, and Aquatica at SeaWorld.

The Alamo Trolley
Need a captivating-yet-low impact activity? Ride the Alamo Trolley. This "hop-on, hop-off" trolley allows you to explore San Antonio at your own pace. With 10 stops around town, this entirely narrated tour includes The Alamo, Hemisfair Park, River Walk, the Mission Trail, and more.

Clyde and Seamore's Sea Lion High
If you go to SeaWorld San Antonio, kids will love attending the sea lion show called "Clyde and Seamore's Sea Lion High." The sea lions perform tricks and interact with the audience as Clyde and Seamore go back to school in search of their diplomas.

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Natural Bridge Cavern

Natural Bridge Caverns
Explore the Natural Bridge Caverns, the largest caverns in Texas. This family-owned and family-operated attraction offers guided and adventure tours, an outdoor maze, mining for gems and fossils, and more! When you're done, you can visit the Shops of Discovery Village where you'll find treats, a general store, and souvenirs to take home.

Brackenridge Park
Spend the day at one of San Antonio's most popular parks, Brackenridge Park. Hike or bike along one of the nature trails, have a picnic, play with your kids at the Kiddie Park, or find the Japanese Tea Garden. Want to add something a little more exciting to your day? The San Antonio Zoo is also on the grounds, where there are lots of animals, experiences, and events.

COLLEEN PENCE/CC 2.0 GENERIC

Aquatica at SeaWorld San Antonio

CHEST NETWORKS

Transcutaneous CO_2 monitoring, updated ILD patient education coming

Airways Disorders

Quadrupling the inhaled glucocorticoid dose in those with deteriorating asthma control: Zone 2 asthma

Asthma exacerbations account for most asthma-associated health-care costs and are a key outcome for successful asthma management programs.

Inhaled corticosteroid (ICS) forms the cornerstone of asthma maintenance therapy.

Previously published data show that:

- Most therapeutic benefit of budesonide was achieved at dose range of 400-1000 µg/day (*Masoli et al. Eur Respir J. 2004;23:552*).
- Doubling ICS dose was ineffective in preventing acute asthma exacerbations (*Harrison et al. Lancet. 2004;363:271. FitzGerald et al. Thorax. 2004;59: 550).*
- Increasing ICS dose was unlikely to reduce systemic glucocorticoid use or hospitalization for asthma exacerbations(*Kew et al. Cochrane Database Syst Rev. 2016;6:CD007524*).

A recent open-label pragmatic study, published in the *New England Journal of Medicine*, included 1,922 adolescents and adults with asthma. The authors observed a small reduction in severe asthma exacerbations (Hazard ratio 0.81 for time to first severe exacerbation) by quadrupling the dose of ICS during periods of worsening asthma control (*McKeever et al. N Engl J Med. 2018;378:902*).

DR. RAMESH

DR. ANAND

This study does create opportunities for cost-benefit by decreasing health-care utilization, decrease in systemic steroid exposure in some patients, and increase in patient awareness of asthma control allowing self-management. Although statistically significant, the treatment effect was small, with 45% of subjects in the 'quadrupling dose' arm still experiencing severe exacerbations. Intervention arm also experienced increased rate of adverse effects.

Additional studies are needed before this strategy can be broadly applied. In the same issue of NEJM, quintupling the dose of ICS in children was not associated with decrease in exacerbations (*Jackson et al. N Engl J Med. 2018;378:891*).

The fact that nearly half of asthmatics who quadrupled ICS dose had exacerbations is disconcerting. This highlights an urgent need to understand treatment-responsive

Continued on following page

Continued from previous page

phenotypes, mechanisms of steroid sensitivity, and modalities to improve them, if we are to reduce asthma morbidity in the community.

Navitha Ramesh, MD
Steering Committee Member
Mahesh Padukudru Anand, MBBS, FCCP
Steering Committee Member

Clinical Research

Informed consent: Do we need to change our practice?

Informed consent is the keystone of clinical research and helps respect and protect the rights of the participants/subjects. While the informed consent process has been standardized, some challenges still remain, such as pieces of information that should be disclosed, how to disclose information and document understanding of participants, and how detailed that disclosure should be (Grady, *N Engl J Med.* 2015;372:855). Digital technology can and has been used to improve the process of obtaining informed consent.


DR. IJAZ

Substituting long and complex written forms with electronic consent (e-consent), however, has issues. Few people read through online agreements before clicking "agree," which may lead to participants consenting without a clear understanding of what they are consenting to.

On the other hand, it is also possible to use e-consent to improve comprehension by including videos and graphics. Interactive quizzes can assess the understanding of the participants, embedded links to audios or videos can further enhance the grasp of information. With e-consents, queries from participants can be answered via phone call or email. When e-consent is obtained remotely, the identity can be confirmed by electronic signatures, username, password, or biometrics.

E-consent has advantages, can be done remotely, no paper is needed, etc. It has potential disadvantages like being costly, videos can add time to the process, and multicenter international trials can be difficult (Grady, et al. *N Engl J Med,* 2017; 376:e43). Studying e-consents to identify gaps in communication between the researcher and the participant in the digitalized world may help improve the process and allow research to proceed with better understanding of the risks and benefits of involvement in clinical research.

Mohsin Ijaz, MD, FCCP
Steering Committee Member

Critical Care

Fluid resuscitation in ICU patients with sepsis

Appropriate fluid resuscitation is a major goal in sepsis management. Debate remains regarding fluid choice and the impact on acute kidney injury (AKI), renal replacement therapy (RRT), and mortality. Normal saline solution (NS) may be associated with hyperchloremic metabolic acidosis, AKI, and death, but study results have been inconsistent.

A large before-after study revealed that balanced crystalloids (BC) were associated with lower rates of AKI and RRT but did not impact mortality (Yunos et al. *JAMA*. 2012;308:1566). A meta-analysis specifically examining patients with sepsis failed to find a significant difference in RRT or mortality, although this conclusion was of low certainty (Rochwerg, et al., *Intensive Care Med.* 2015;41:1561).


DR. DISSELKAMP

Earlier this year, a large RCT comparing NS vs BC demonstrated a reduction in major adverse kidney events using BC. Independent rates of new RRT, mortality, and persistent renal dysfunction were not significant, but when combined as a composite outcome, the difference was significant. A 30-day mortality reduction was significant in patients with sepsis (25.2% BC vs 29.4% NS) and in patients with large infusions of NS (Semler et al., *N Engl J Med*. 2018;378:829).

Given these results, a move toward a "balanced approach" to fluid resuscitation seems prudent and may be the next step toward im-

proving outcomes in sepsis. These results are likely related to the large infusions of fluid in patients with sepsis or to the inflammatory effects of the disease. Finally, the applicability of these outcomes to the overall critically ill population is still open to debate.

Margaret Disselkamp, MD
Steering Committee Member

Home-Based Mechanical Ventilation and Neuromuscular Disease

Transcutaneous carbon dioxide monitoring: New era for home ventilation

A primary objective of noninvasive home ventilation is normalization of arterial blood gas tensions, night and day. Pulse oximetry has long enabled estimation of arterial oxygen saturation (SpO_2) in outpatient offices and overnight at home; however, until recently, measurement of the partial pressure of carbon dioxide (PCO_2) has been limited to invasive arterial blood gas testing ($PaCO_2$) or end-tidal CO_2 ($PetCO_2$) measurements.


DR. ACKRIVO

Assessment of $PetCO_2$ has been limited by challenges in accessing true end-tidal exhaled gas under a face mask during noninvasive ventilation, particularly for patients with parenchymal lung diseases such as COPD.

Thanks to recent technological advances, transcutaneous measurement of carbon dioxide ($PtcCO_2$) is emerging as the method of choice for assessing the adequacy of noninvasive ventilation. $PtcCO_2$ monitoring is a standard assessment for pediatric patients in the sleep lab, and it is increasingly being utilized in adults to complement diagnostic and treatment purposes.

The transcutaneous CO_2 sensors work by heating underlying skin to approximately 43° C, increasing blood flow through the underlying dermal capillary bed. Within 2 to 5 minutes, the "arteriolized" capillary $PtcCO_2$ approximates $PaCO_2$.

Commercially available devices for measuring $PtcCO_2$ reliably estimate $PaCO_2$ in patients undergoing noninvasive ventilation to within 5 mm Hg (95% CI) (Storre et al. Respir Med. 2010;105:143).

$PtcCO_2$ measurement has limitations. Measured $PtcCO_2$ can drift upward (i.e., technical drift) during continuous monitoring; however, currently available devices adequately adjust for this phenomenon. Arterialization may be limited by thickened skin, edema, or hypoperfusion.

Currently, U.S. insurance companies do not accept $PtcCO_2$ for documentation of hypercapnia, and the cost of measuring $PtcCO_2$ is not reimbursed. Nevertheless, $PtcCO_2$ technology promises a new era for home mechanical ventilation guided by accurate and practical assessment of PCO_2, in particular for chronic respiratory failure syndromes. In this setting, home $PtcCO_2$ monitoring potentially can be utilized in place of in-laboratory sleep studies for assessment of nocturnal hypoventilation and optimizing home mechanical ventilation.

Jason Ackrivo, MD
Steering Committee Member

Interstitial and Diffuse Lung Disease

Electronic patient education

The management of patients with an interstitial lung disease (ILD) is challenging. A provider must examine the fine details about current and prior medication history, explore various occupational and environmental exposures, perform a thorough physical examination that includes a careful dermatologic and rheumatologic review, and peruse the objective data, such as the high-resolution CT scan of the chest and pulmonary function tests. Then, the pulmonologist and the patient (plus often multiple family members) discuss diagnostic possibilities, any future testing for confirmation, and prognostic implications. Understandably, the patient may leave the office bewildered, overwhelmed, and in search of clarification.


DR. KERSHAW

Bewilderment may lead to the internet. In 2001, 4.5% of all internet searches were determined to be health-care-related (Eysenbach et al. *AMIA Annu Symp Proc.* 2003;225).

It is reasonable to presume the percentage is higher today. Just as with any nonmedical website, the choices for digital health-care information are sometimes not contemporaneous and vary in quality. By exploring the most common "hits" on popular search engines when searching for idiopathic pulmonary fibrosis, a 2016 study found that not only is information presented at a high reading level – 12th grade – but often outdated or simply wrong (Fisher, et al. *Am J Respir Crit Care Med.* 2016;194[2)]:218).

Adding to a patient's possible confusion is that websites expected to be the most helpful, foundation or advocacy websites, were more likely to suggest disproven and even harmful therapies years after those conclusions were published.

CHEST and the Interstitial and Diffuse Lung Disease NetWork are committed to patient education both in and out of the clinical setting.

An ongoing redesign of ILD patient education on the CHEST Foundation website is nearing completion and will ensure patients have the most accurate and understandable information available.

Corey Kershaw, MD
Steering Committee Member

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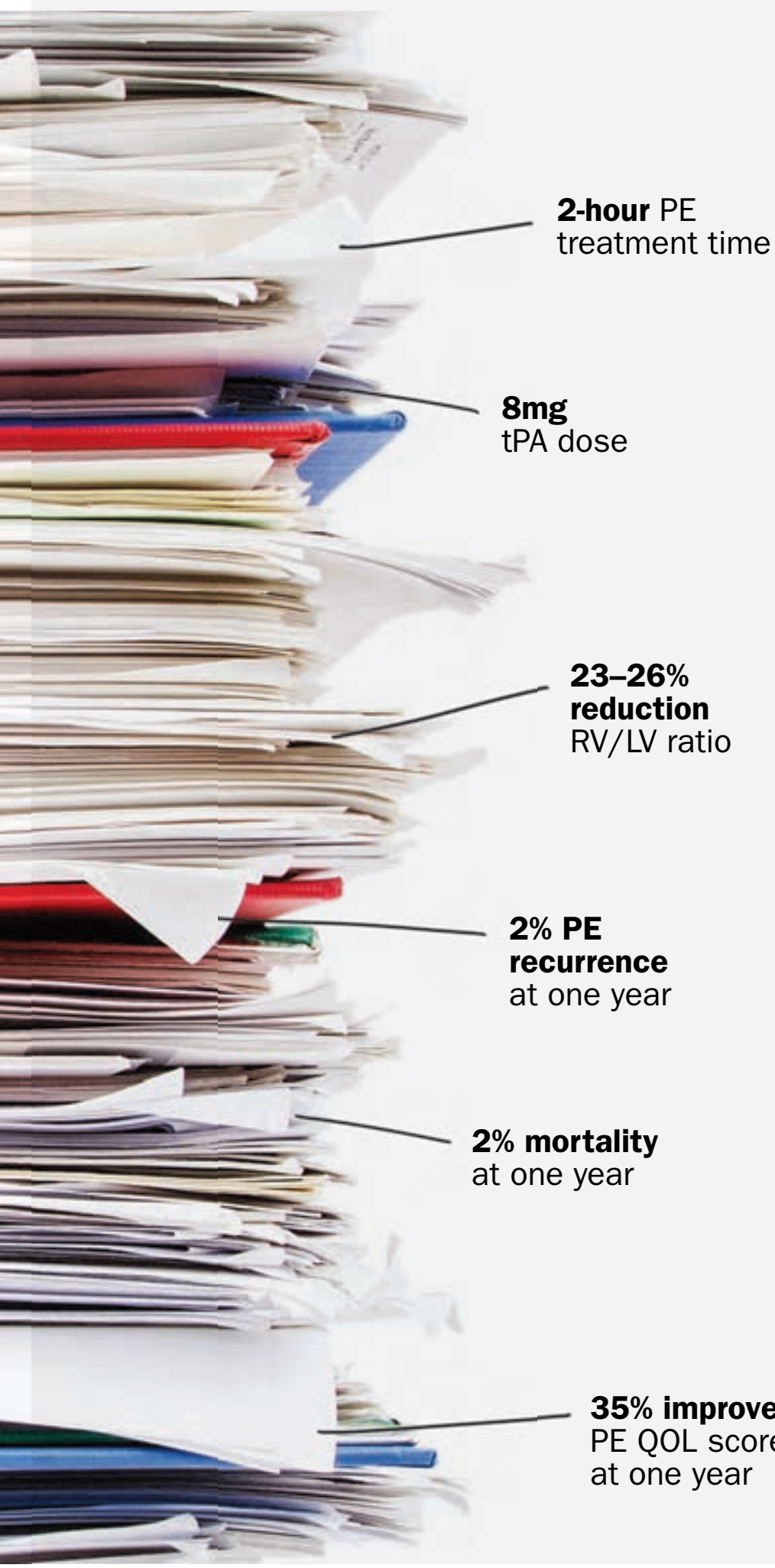

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*Sterling, K. "Long-term Results of the OPTALYSE PE trial" as presented at the International Symposium on Endovascular Therapy (ISET) meeting, Hollywood, FL. Feb 2018.

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