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Courtesy Jim Rieker

Dr. Jin's coauthors included Dr. Raghavan Murugan, Dr. Gilles Clermont, and Priyanka Priyanka (pictured from left to right).

Intense urine output monitoring beneficial in ICU

BY IAN LACY
Frontline Medical News

FROM CHEST ▪ Intense monitoring of urine output could be a useful tool in detecting acute kidney injury (AKI), according to a study conducted at the University of Pittsburgh.

Kui Jin, MD, of the University of Pittsburgh and his associates found that, after adjustment for baseline characteristics, intensive monitoring of urine output (UO) was associated with higher rates of AKI, with an odds ratio of 1.22. Intensive UO monitoring also was strongly associated with improved 30-day survival among patients developing AKI.

"Treatment for AKI is focused on supportive care and identification of the underlying etiology. Both of these priorities might be improved by earlier detection of AKI and closer monitoring of kidney function," wrote Dr. Jin and his associates.

This retrospective cohort study included 15,724 adult patients admitted to the center's ICUs during 2000-2008. All patients had either their UO or serum creatinine (SC) monitored. These patients were then divided into subcohorts that were monitored at one of two different intensities. UO intensive monitoring was defined by hourly recordings, with gaps no greater than 3 hours for the first 48 hours after ICU admission. The group receiving less intensive UO monitoring comprised patients who did not

ACUTE KIDNEY INJURY DETECTED // *continued on page 6*

Regionalized STEMI care slashes in-hospital deaths

BY BRUCE JANCIN
Frontline Medical News

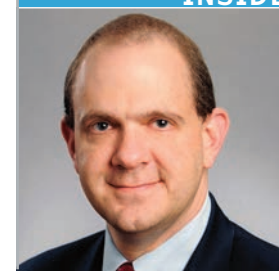
ANAHEIM, CALIF. – An American Heart Association program aimed at streamlining care of patients with ST-elevation MI resulted in a dramatic near-halving of in-hospital mortality, compared with STEMI patients treated in hospitals not participating in the project, James G. Jollis, MD, reported at the American Heart Association scientific sessions.

He presented the results of the STEMI ACCELERATOR 2 study, which involved 12 participating metropolitan regions across the United States, 132 percutaneous coronary intervention–capable hospitals, and 946 emergency medical services agencies. The ACCELERATOR 2 program entailed regional implementation of a structured STEMI care plan in which EMS personnel were trained to obtain prehospital ECGs and to activate cardiac catheterization labs prior to hospital arrival, bypassing the emergency department when appropriate.

Key elements of the project, which was part of the AHA's Mission: Lifeline program, included

TIME-TO-CARE MEASURES IMPROVED // *continued on page 4*

INSIDE HIGHLIGHT



NEWS FROM CHEST

Get to know *CHEST Physician*'s new leaders

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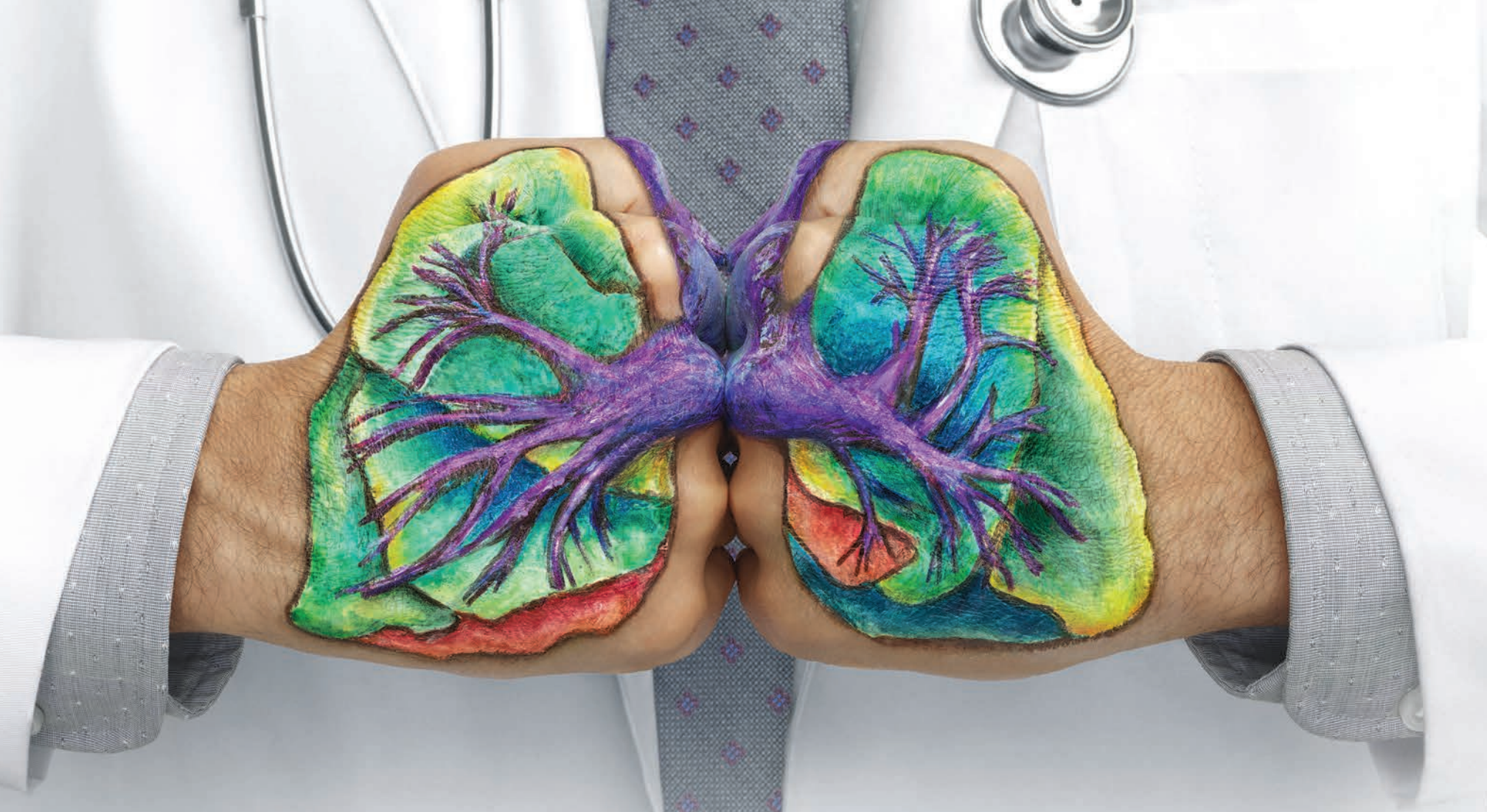

Indication

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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Help preserve more lung function. Reduce lung function decline.[1–4]

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Clinical trials included patients with IPF with a range of clinical characteristics, select comorbidities, and concomitant medications[1]

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials[2†]

COMMITTED TO PATIENTS

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

WORLDWIDE PATIENT EXPERIENCE

More than 31,000 patients have taken pirfenidone worldwide[1§]

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

Time-to-care measures improved // *continued from page 1*

having participating hospitals measure their performance of key processes and send that information as well as patient outcome data to the National Cardiovascular Data Registry's ACTION–Get With The Guidelines registry. The hospitals in turn received quarterly feedback reports containing blinded hospital comparisons.

The impetus for the STEMI ACCELERATOR 2 project was simple: "Every day in the United States, people die because of the fragmented nature of emergency cardiac care," declared Dr. Jollis, a cardiologist at Duke University in Durham, N.C.

Dr. Jollis and his coinvestigators worked to obtain buy-in from local stakeholders, organize regional leadership, and help in drafting a central regional STEMI plan featuring prespecified treatment protocols.

The STEMI ACCELERATOR 2 study was carried out in 2015-2017, during which 10,730 patients with STEMI were transported directly to participating hospitals with PCI capability.

The primary study outcome was the change from the first to the final quarter of the study in the proportion of EMS-transported patients with a time

from first medical contact to treatment in the cath lab of 90 minutes or less. This improved significantly, from 67% at baseline to 74% in the final quarter. Nine of the 12 participating regions reduced their time from first medical contact to treatment in the cath lab, and eight reached the national goal of having 75% of STEMI patients treated within 90 minutes.

The other key time-to-care measures improved, too: At baseline, only 38% of patients had a time from first medical contact to cath lab activation of 20 minutes or less; by the final quarter, this figure had climbed to 56%. That's an important metric, as evidenced by the study finding that in-hospital mortality occurred in 4.5% of patients with a time from first medical contact to cath lab activation of more than 20 minutes, compared with 2.2% in those with a time of 20 minutes or less.

Also, the proportion of patients who spent 20 minutes or less in the emergency department improved from 33% to 43%.

In-hospital mortality improved from 4.4% in the baseline quarter to 2.3% in the final quarter. No similar improvement in in-hospital mortality occurred in a comparison group of 22,651 STEMI patients treated at hospitals not involved in ACCELERATOR 2.

A significant reduction in the rate of in-hospital congestive heart failure occurred in the ACCELERATOR 2 centers, from 7.4% at baseline to 5.0%. In contrast, stroke, cardiogenic shock, and major bleeding rates were unchanged over time.

The ACCELERATOR 2 model of emergency cardiovascular care is designed to be highly generalizable, according to Dr. Jollis.

"This study supports the implementation of regionally coordinated systems across the United States to abort heart attacks, save lives, and enable heart attack victims to return to their families and productive lives," he said.

The ACCELERATOR 2 operations manual – essentially a blueprint for organizing a regional STEMI system of care – is available gratis.

Discussant Larry A. Allen, MD, applauded the investigators for shifting the focus of quality improvement efforts in STEMI care away from a fixation on door-to-balloon time. That measure, while important, constitutes only one element in the STEMI care system. The clock really ought to start ticking at the time of first medical contact. And emergency department waiting time is an important indicator of coordination of care between paramedics and hospitals.

Dr. Allen, a cardiologist at the University of Colorado, Denver, said the ACCELERATOR 2 model has been successful because it is consistent with a fundamental principle of implementation science as described by Carolyn Clancy, MD, Executive in Charge at the Veterans Health Affairs Administration, who has said it's a matter of making the right thing to do the easy thing to do. Gregg C. Fonarow, MD, founder of the Get With The Guidelines program and professor and cochief of cardiology at the University of California, Los Angeles, predicted that the success of this program will lead to a ramping up of efforts to regionalize and coordinate STEMI care across the country. Simultaneous with the presentation at the AHA conference, the results of STEMI ACCELERATOR 2 were published online in Circulation (2017 Nov 14. doi: 0.1161/CIRCULATIONAHA.117.032446).

The trial was sponsored by research and educational grants from AstraZeneca and The Medicines Company. Dr. Jollis reported having no financial conflicts of interest.

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Acute kidney injury detected

// continued from page 1

meet intensive monitoring criteria, regardless of their UO in the 7 days following ICU admission. The patients who had their SC intensively monitored had 3 calendar days of samples taken after their ICU admissions. Those who did not meet SC intensive monitoring criteria were placed into the less intensive SC monitoring group.

To understand the effect of the monitoring strategies on detecting the development of AKI, the researchers determined each patient's baseline, admission, and reference serum creatinine levels. Baseline creatinine was defined as the lowest value in the year prior to hospital admission. The source for a patient's reference creatinine varied; for example, for some patients reference creatinine represented the lowest creatinine level recorded within 24 hours after ICU admission or the baseline value.

The crude rates of stage 2-3 AKI 7 days after admission to the ICU were similar between patients from both groups who had their UO monitored; 62.5% of intensive and 63.9% of less intensive patients displayed symptoms. After the researchers adjusted for baseline characteristics, however, intensive monitoring of UO was associated with greater rates of stage 2-3 AKI (OR, 1.22; *P* less than .001). Crude rates were higher in the patients who received intensive monitoring for SC, compared with patients who received less intensive monitoring for SC.

Ultimately, Dr. Jin and his associates found when caring for patients with or without AKI, fluid management is one of the most important factors. Patients who underwent intensive UO monitoring received less fluid in their first 24 hours (3.6 L) in the ICU, compared with patients who received less intense UO monitoring (4.2 L). Patients who received intensive monitoring of their UO also were less likely to use vasopressors (29.9% vs. 43.3%; *P* less than .001), suggesting these patients were more hemodynamically stable. Further, the percentage of patients at or above 10% of fluid overload was lower in the group who received intensive monitoring of their UO (2.49% vs. 5.68%; *P* less than .001) during the first 72 hours in the ICU.

C.R. Bard provided partial funding for this study.

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VIEW ON THE NEWS

Nikita Desai, MD, and William S. Bender, MD, of Emory University School of Medicine, comment: Dr. Jin and colleagues seek to answer several important clinical questions: "Do people live longer if we monitor their urine output closely? Is this because we are detecting acute kidney injury sooner? Does managing fluid balance seem to be the critical intervention in impacting mortality?" In an era where hospital reimbursements are diminishing with the diagnosis of catheter-associated urinary tract infection, these are laudable inquiries.

In this study, patients who presented with acute kidney injury and had their urine output monitored hourly had a lower hazard for 30-day mortality when compared to those patients who did not have urine output monitored closely (HR 0.85 [0.77 – 0.94] versus HR 0.90 [0.81 – 0.99]). The authors posit this may be secondary to better management of fluid balance since the former group had less total fluid accumulation. However, in patients without acute kidney injury, this difference is not detected, and the authors do not include the HR for this subset of patients.

The authors reveal that those patients without acute kidney injury who have their serum creatinine monitored daily seem to have a hazard ratio of 30-day mortality of 0.70 (0.60 – 0.80). However, when these same patients are adjusted for age and acuity of illness, this difference in mortality seems to disappear (HR 1.20 [1.18 – 1.21]). While adjusted outcomes are often altered when managing so many co-variates, this trend toward worsening mortality lessens confidence in the authors' conclusions.

In studies which examine such a large cohort of patients, some differences in mortality and morbidity will inevitably be detected. However, clinicians should be very cautious to make changes in clinical practice based on the results of trends in these data sets. These studies are not designed to demonstrate causality for any meaningful associations, and should be confirmed with clinical trials. Database studies such as this one continue to have their value in hypothesis generation, which will guide future critical care research.

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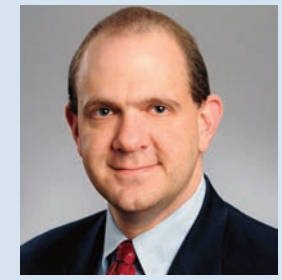

David A. Schulman, MD, FCCP, is Medical Editor in Chief of CHEST Physician.

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CardioMEMS shows real-world success as use expands

BY MITCHEL L. ZOLER
Frontline Medical News

DALLAS – Management of outpatients with advanced heart failure using an implanted pulmonary artery pressure monitor continues to show real-world efficacy and safety at least as impressive as in the pivotal trial for the device.

Data from the first waves of patients to receive the CardioMEMS implanted pulmonary artery pressure (PAP) monitor since it got Food and Drug Administration marketing approval in May 2014 also showed steady uptake of this fluid volume management strategy for patients with advanced heart failure, despite Medicare reimbursement issues in some U.S. regions, J. Thomas Heywood, MD, said at the annual scientific meeting of the Heart Failure Society of America. He estimated that more than 6,000 U.S. heart failure patients have now had a CardioMEMS PAP monitor implanted.

Dr. J. Thomas Heywood

Dr. Joanna M. Joly

Mitchel L. Zoler/Frontline Medical News

"PAP monitoring seems to work in the real world," said Dr. Heywood, a heart failure cardiologist at the Scripps Clinic in La Jolla, Calif. An apparent signal of better patient outcomes during routine use, compared with outcomes in the pivotal CHAMPION trial (Lancet. 2011 Feb 19;377[9766]:658-66), may reflect a real change in how clinicians use the data from implanted PAP monitors, he speculated.

"The clinicians using CardioMEMS now have a lot more experience" than they had during the trial, he said in an interview. "They have more experience using the device, they know what treatments to use to lower PAP more effectively, and they are now convinced that patients will benefit from reducing diastolic PAP."

Dr. Heywood estimated that tens of thousands more U.S. heart failure patients with New York Heart Association class III disease and a recent history of at least one heart failure hospitalization are eligible to receive an implanted PAP monitor, dwarfing the more than 6,000 patients who received a device so far.

The postapproval study

The newest efficacy data come from the first 300 patients enrolled in the CardioMEMS HF System Post Approval Study, a registry of patients receiving an implanted PAP monitor funded by the device's manufacturer and scheduled to include a total of 1,200 patients. Dr. Heywood said full enrollment was on track for completion by the end of October 2017.

The first 300 patients enrolled in the postapproval study were older than the CHAMPION cohort. They averaged about 69 years of age, compared with about 62 years in CHAMPION; were more often women (38% vs. 28% in CHAMPION); and were more likely to have heart failure with preserved ejection fraction (41% vs. about 22%).

Follow-up data showed that, during the first 6 months with PAP monitoring, the 300 patients averaged 0.20 hospitalizations for worsening heart failure, with 56 hospitalizations in 43 patients (14%), reported Nirav Y. Raval, MD, a cardiologist at Florida Hospital in Orlando. In contrast, in CHAMPION the average heart failure hospitalization rate during 6 months was 0.44 in control patients and 0.32 in those managed using frequent monitoring of an implanted PAP device.

A similar pattern existed for the 6-month cumulative tally of PAP area under the curve, which showed an average rise of 42 mm Hg/day in the CHAMPION control patients, an average drop of 160 mm Hg/day in the CHAMPION patients managed using their CardioMEMS data, and a drop of 281 mm Hg/day in the 300 postapproval study patients.

"We're now using the implanted sensor in a broader population of patients, and one wonders whether the effect will be diluted. What we see is at least as good as in the CHAMPION trial. This is just an early snapshot, but it is exciting that we see no erosion of the benefit. It's a great indication that the correct patients are receiving it," Dr. Raval said while presenting a poster at the meeting.

Further scrutiny of the same 300 patients showed another feature of the impact of PAP monitoring on patient outcomes: The first 90 days with the PAP monitor in place led to a greater number of tweaks in patient treatment and a steady fall in PAP. During days 91-180, PAP tended to level off, the number of medication adjustments dropped, and heart failure hospitalizations fell even more than in the first 90 days, Joanna M. Joly, MD, reported in a separate poster at the meeting.

During days 0-90, heart failure hospitalizations averaged a 6-month rate of 0.29, but during days 91-180 this dropped to an average 6-month rate of 0.11, said Dr. Joly, a cardiologist at Brigham and Women's Hospital in Boston. Also during the first 90 days, the 300 patients underwent 1,226 medication changes, most often drug up-titrations with a diuretic or with nitrates. During days 91-180, this fell by nearly half, to 660 medication changes, a rate of 2.2 changes per patient during the second set of 90 days or fewer than 1 medication change per month in each patient, she reported.

The data showed "effective reduction" of PAP during the second half of the study despite fewer medication adjustments. How was that possible? Patients who transmit data on their PAPs undergo "modeling of their behavior" based on the feedback they receive from the device, Dr. Joly suggested. Regular measurement of their PAP and seeing how the number relates to their clinical status helps patients "understand the impact of their nonadherence to diet and their medications." Another factor could be the growing familiarity clinicians develop over time with PAP fluctuations that individual patients display repeatedly that are usually self-correcting. Also, patients may undergo "hemodynamic remodeling" that results in improved self-correction of minor shifts in fluid volume and vascular tone, she said.

This pattern of a reduced need for interventions after the first 90 days with a PAP implant suggests that many patients managed this way may be able to transition to care largely delivered by local providers, or even play a greater role in their own self-care once their PAP and clinical state stabilizes, Dr. Joly said.

The findings imply that by the end of the first 90 days, "patients accept the device and manage themselves better. It becomes basically a behavioral device" that helps patients better optimize their diet and behavior, Dr. Raval observed.

Safety holds steady

Continued real-world use of PAP monitoring has also resulted in new safety insights. During the first 3 years when the CardioMEMS device was on the U.S. market, May 2014–May 2017, the FDA's adverse event reporting system for devices, the Manufacturer and User Facility Device Experience (MAUDE), received reports on 177 unique adverse events in 155 patients implanted with a PAP monitor, Muthiah Vaduganathan, MD, reported at the meeting. During the same 3-year period, he estimated that at least 5,500 U.S. patients had received a CardioMEMS device, based on data Dr. Vaduganathan obtained from the manufacturer, Abbott. This works out to an adverse event rate of about 2.8%, virtually identical to the rate reported from CHAMPION, noted Dr. Vaduganathan, a cardiologist also at Brigham and Women's.

The most common adverse event was a sensor failure, malfunction, or migration, which happened in 26% of the patients, followed by pulmonary artery injury or hemoptysis, which occurred in 16%. MAUDE reports for the device included 22 deaths, including six patients who died as a result of pulmonary artery injury or hemoptysis, four patients who died from a heart failure–related

Continued on following page

Bilateral ACP shown similar to unilateral in study

BY RICHARD MARK KIRKNER
Frontline Medical News

What may be the largest study comparing unilateral and bilateral antegrade cerebral perfusion during total arch replacement (ACP) for type A aortic dissection has reported that outcomes between the two approaches are comparable, although the bilateral approach showed some advantages during the operation itself, investigators from China reported in the Journal of Thoracic and Cardiovascular Surgery (2017;154:767-75).

The effectiveness of bilateral antegrade cerebral perfusion (b-ACP) vs. unilateral antegrade cerebral perfusion (u-ACP) has been the focus of extensive debate, lead study author Guang Tong, MD, of the Guangzhou (China) General Hospital, and coauthors said. They compared outcomes in six different metrics, ranging from cardiopulmonary bypass time to length of stay (LOS) in the ICU and hospital, in 203 patients with type A aortic dissection who had total aortic arch replacement with hypothermic circulatory arrest over an 8-year period ending in August 2014; 121 had b-ACP and 82 had u-ACP. "The issue of u-ACP vs. b-ACP has been examined in aortic arch surgery, but few reports have focused on type A aortic dissection," Dr. Tong and coauthors wrote.

They acknowledged that some surgeons are reluctant to use b-ACP because of its complexity, but their study found no increase in cross-clamp time, cardiopulmonary bypass time, or surgery time in the b-ACP group. They cited another reason surgeons give for avoiding b-ACP: the risk of embolic injury caused by canulating the left common carotid artery in an atheromatous aorta. "In the present study, this risk was avoided by attaching the left common carotid artery to the four-branched prosthetic graft for left hemisphere perfusion," Dr. Tong and coauthors wrote.

Key outcomes that the researchers found not statistically significant were:

- Overall 30-day mortality (11.6% for b-ACP vs. 20.7% for u-ACP; $P = .075$).
- Prevalence of postoperative permanent neurologic dysfunction (8.4% vs. 16.9%; $P = .091$).
- Average ICU LOS (16 ± 17.75 days vs. 17 ± 11.5 days, $P = .454$).
- Average hospital LOS (26.5 ± 20.6 days vs. 24.8 ± 10.3 days, $P = .434$).

However, average ventilation time was lower in the b-ACP group (95.5 hours vs. 147 hours; P less than or equal to .001).

Dr. Tong and coauthors used an aggressive approach, as advocated by Dhaval Trivedi, MD, and colleagues (Ann Thorac Surg. 2016;101:896-903), and had a total arch replacement rate of 57.8%. This rate is higher than most published series in the West but comparable to other studies from China, perhaps because of the relatively young age of this study cohort – an average age of 51 years – compared to data sets other studies have used. Dr. Tong and coauthors used a b-ACP strategy that established both cerebral perfusion routes before circulatory arrest.

Rates of the following complications were also not significantly different across the study population: paraplegia (2.8% for b-ACP vs. 3.1% for u-ACP), temporary neurologic dysfunction (4.7% vs. 9.2%), permanent neurologic dysfunction (TND) (8.4% vs. 16.9%), renal failure (18% vs. 23.1%), reoperation for bleeding (2.8% vs. 4.6%), and mediastinal infection (3.7% vs. 6.2%).

While b-ACP patients did not have a statistically significant lower incidence of TND, Dr. Tong and coauthors noted the shorter time on ventilation and significantly lower tracheostomy rates for the b-ACP patients, 3.7% vs. 16.9% for the u-ACP group ($P = .003$). "In our institute, protocols to wean patients from ventilation were normally initiated as soon as consciousness was regained," Dr. Tong and coauthors wrote. Among the study limits were its retrospective, nonrandomized, single-center nature.

The investigators reported having no relevant financial disclosures.

VIEW ON THE NEWS

Still waiting for an answer

The study by Dr. Tong and coauthors adds to the discussion between the "bilateralists" and "unilateralists," as Jean Bachet, MD, called the two prevailing camps on cerebral perfusion strategies in his invited commentary (J Thorac Cardiovasc Surg. 2017;154:765-6). And while most clinical reports find outcomes similar between the two approaches, the evidence favors the bilateral approach for total arch replacement.

Citing how the study implied mortality and neurologic morbidity rates almost half those for unilateral perfusion, but not reaching statistical significance, Dr. Bachet said, "The statisticians would say that this is only a trend and no proof, but some trends might be indicative, and significance might only be a matter of number in each arm of the comparison."

Dr. Bachet raised a question about the unilateral approach – that once the arch is opened it takes a minute or so to insert the small balloon canula into the origin of the left carotid artery or divided vessel and start bilateral perfusion. "A major question arises," said Dr. Bachet: "Why should we expose our patients to any undue risk just to avoid a simple maneuver, to spare a little time, or for any other fancy and questionable reason?"

Cardiologists have raised that question for more than 20 years. Said Dr. Bachet, "We still wait for the answer."

Dr. Bachet is a cardiac surgeon in Surgenes, France. He reported having no financial relationships to disclose.

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cause, and 12 patients with death from an unknown cause or a cause unrelated to their heart failure or CardioMEMS placement.

Analysis of both the 22 deaths as well as the episodes of pulmonary artery injury or hemoptysis showed that the preponderance occurred relatively early after introduction for U.S. use, suggesting that "a learning curve may exist for the most serious complications," he said. "Improved safety and device durability may result from careful patient selection, increased operator training, and refined technologies."

Dr. Vaduganathan cautioned that the MAUDE database is limited by its bias toward serious adverse events, selective reporting, and lack of adjudication for the reported events. Concurrently with his report at the meeting, a written version appeared online (JAMA Cardiol. 2017 Sep 18. doi:10.1001/jamacardio.2017.3791).

"The adverse event rate was reassuringly low, well below the accepted threshold for device safety. It bodes favorably for the device," he said in an interview.

"But with a passive surveillance system like MAUDE, adverse events are likely underreported; we see in MAUDE the most severe adverse events. There is certainly a larger spectrum of more minor events that we are not seeing, but I think these numbers accurately reflect serious events." A full registry of every U.S. patient who receives the device, similar to what's in place for U.S. patients who undergo transcatheter aortic valve replacement, would provide a more complete picture of the risks, Dr. Vaduganathan suggested.

He also voiced some surprise about the frequency of pulmonary artery injury, which was not as apparent in the 550 total patients enrolled in CHAMPION. Clinicians who place the PAP monitor are required to first take a training program, but the manufacturer has no mandated minimum number of placements an operator must assist on before launching a new CardioMEMS practice, Dr. Vaduganathan said. Many of the pulmonary artery injuries reported to MAUDE resulted from wire perforations that resulted from loss of wire control, he noted. Dr. Heywood said that, in addition to the standard criteria of NYHA class III symptoms and a recent history of a heart failure hospitalization, the other clinical feature he looks for in a patient who is a possible CardioMEMS recipient is a persistently elevated systolic PAP as measured using echocardiography.

The CardioMEMS HF System Post Approval Study is sponsored by Abbott, which markets CardioMEMS. Dr Heywood has been a consultant to and/or has received research funding from Abbott as well as Impedimed, Medtronic, Novartis, and Otsuka. Dr. Raval has been a consultant to Abbott. Dr. Joly and Dr. Vaduganathan had no disclosures.

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

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

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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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.

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE
TRELEGY is a combination inhaled corticosteroid/anticholinergic/long-acting beta$_2$-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.
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 patients with severe hypersensitivity to milk proteins or who have 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 Asthma-Related Death
Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death.
A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in TRELEGY.
No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with TRELEGY has been conducted. The safety and efficacy of TRELEGY in patients with asthma have not been established. TRELEGY is not indicated for the treatment of asthma.
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
TRELEGY contains fluticasone furoate, an inhaled corticosteroid (ICS). Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products, including fluticasone furoate. 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 less than 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 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 (less than 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 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 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

cont'd

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 develops. 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 develops.

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

LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

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

- *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 coadministration of umeclidinium and the fixed-dose combination of fluticasone furoate and vilanterol and on the long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, the fixed-dose combination of umeclidinium/vilanterol, and umeclidinium monotherapy *[see Description (11), Clinical Pharmacology (12.3), and Clinical Studies (14.1) of full prescribing information].*

Confirmatory Trials

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 (14.1) 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 upon the two 12-week trials.

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

Supporting Long-Term Safety Data

The long-term (≥12 months) safety profiles from the fixed-dose combination of fluticasone furoate/vilanterol, umeclidinium/vilanterol, and umeclidinium monotherapy are similar to that reported in the 12-week clinical trials described in Table 1. *[See full prescribing information for BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder), and INCRUSE ELLIPTA (umeclidinium inhalation powder).]*

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. *[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 9 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 100 and 25 mcg in adults, respectively. *[See Data.]* Umeclidinium administered via inhalation or subcutaneously to pregnant rats and rabbits was not associated with adverse effect on embryofetal development at exposures approximately 50 and 200 times, respectively, the human exposure at the MRHDID.

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the US 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

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.

Data

Animal Data: The combination of fluticasone furoate, umeclidinium and vilanterol has not been studied in pregnant animals. Studies in pregnant animals have been conducted with fluticasone furoate and vilanterol in combination and individually with fluticasone furoate, umeclidinium or vilanterol.

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 9 and 40 times the MRHDID, respectively, alone or in combination (on a mcg/m2 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 9 and 2 times the MRHDID, respectively (on a mcg/m2 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 3 times the MRHDID (on a mcg/m2 basis at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed.

Umeclidinium: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received umeclidinium via inhalation during the period of organogenesis at doses up to approximately 50 and 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No evidence of teratogenic effects was observed in either species. In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late gestation and lactation periods at doses up to approximately 26 times the MRHDID (on an AUC basis at maternal subcutaneous doses up to 60 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/m2 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/m2 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, umeclidinium, or vilanterol in human milk; the effects on the breastfed child; or the effects on milk production. Umeclidinium is present in rat milk *[see Data]*. 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.

Data

Animal Data: Subcutaneous administration of umeclidinium to lactating rats resulted in a quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium in rat milk.

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. 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.

cont'd

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]*.
8.7 Renal Impairment
TRELEGY has not been studied in subjects with renal impairment. Information on the individual components is provided below.
Fluticasone Furoate/Vilanterol
There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (CrCl less than 30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3) of full prescribing information]*.
Umeclidinium
Patients with severe renal impairment (CrCl less than 30 mL/min) showed no relevant increases in C_{max} or AUC, nor did protein binding differ between subjects with severe renal impairment and their healthy controls. 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 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 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 (Medication Guide and Instructions for Use *of full prescribing information*).
Asthma-Related Death
Inform patients that LABA, such as vilanterol, one of the active ingredients in TRELEGY, increase the risk of asthma-related death. TRELEGY is not indicated for the treatment of asthma.
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, 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, it should be treated 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 develops.
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 develops.
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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Knowledge Check-In redo allowed in all subspecialties

BY GREGORY TWACHTMAN
Frontline Medical News

The American Board of Internal Medicine is extending its "no consequence" Knowledge Check-In attempt to all subspecialties.

ABIM previously announced that, beginning in 2018, physicians taking the Knowledge Check-In in 2018 would get another chance to take it in 2 years if they were unsuccessful, even if they were due to pass the maintenance of certification (MOC) exam later that year. In 2018, Knowledge Check-Ins will be offered in internal medicine and nephrology.

"Based on feedback ABIM has received from the physician community, we are happy to let you know that we are extending this policy to include all other internal medicine subspecialties in the future," ABIM said in a Dec. 4 announcement on its website. "This means that if a physician takes the Knowledge Check-In in the first year it is offered in their subspecialty and is unsuccessful, they will get at least one additional opportunity to take and pass it 2 years later."

The Knowledge Check-In is an alternative to the traditional MOC process, and is administered every 2 years rather than the standard decade between MOC exams. ABIM noted that a single failure on a Knowledge Check-In will not result in a status change to a physician's certification status.

> *"[We] are happy to let you know that we are extending this policy to include all other internal medicine subspecialties in the future."*

Separately, ABIM also announced that it will continue to make practice assessment activities (part IV of the MOC program) a part of the portfolio of options that can be used to satisfy MOC requirements.

"Our intent is to support physicians completing MOC activities that are most meaningful to their practice, including those that enhance and improve medical knowledge, as well as many existing quality improvement activities, and those that blend both," ABIM said in its announcement.

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Drug prices a key focus of Senate HELP interview of Azar

BY GREGORY TWACHTMAN
Frontline Medical News

AT A SENATE HELP COMMITTEE HEARING ▪

WASHINGTON – Escalating drug prices topped the agenda as members of the Senate Health, Education, Labor & Pensions Committee interviewed Alex Azar regarding his nomination as secretary of the Department of Health & Human Services.

Mr. Azar, a former HHS deputy secretary and general counsel during the Bush administration and a former president of Eli Lilly's U.S. operations, outlined his priorities to the Senate HELP Committee during a hearing.

MR. AZAR

"With a department the size of HHS, it is often difficult to prioritize. Nonetheless, should I be confirmed, I do envision focusing my personal efforts in four critical areas," including lowering drug prices, improving health care access and affordabilty, paying for outcomes, and tackling the opioid crisis.

Drug prices were the focus of many senators' questions, and while many contentious questions came from panel Democrats, Sen. Rand Paul (R-Ky.) signaled he was not yet on board with his approval for Mr. Azar's nomination.

"I think many [Americans] perceive [that drug companies use] their economic might to manipulate the system to maximize profits," Sen. Paul said. "It's not like they are selling a cheaper product to more people. They are using government to maximize their profits. Do you acknowledge that, under the current system, Big Pharma uses their economic clout to manipulate the patent system to increase drug prices?"

"There are clearly abuses, Senator, in the system, and that is why one of the steps that I mentioned ... that I believe we have to go after, is the gaming of that," Mr. Azar responded. He suggested that although Hatch-Waxman rules give innovators a time frame to exclusively sell products "there should be a certain moment" when full generic competition should begin.

Sen. Paul also challenged Mr. Azar on the notion of drug importation.

There has not been a successful path to certify that drugs being imported are "safe and reliable," Mr. Azar noted.

Sen. Paul countered that "you would have to sit there and say that the European Union has unsafe drugs. It would be unsafe for Americans to buy drugs from the European Union or from Canada or Australia. It's just frankly not true."

Sen. Paul told Mr. Azar that if he cannot come up with a way to reimport drugs as a means of addressing the high cost of pharmaceuticals in the United States, "I can't support you."

Sen. Paul continued that a lot of people have talked about how they are going to change the system, particularly patent issues that stand in the way of generic competition, and "you've got some convincing to make me believe that you are going to represent the American people and not Big Pharma, and I know that's insulting, and I don't mean it to be because I am sure you are an honest and upright person. But we all have our doubts because Big Pharma manipulates the system to keep prices high. ... We've got to fix it. We can't tepidly go at it. We have to really fix it, and you need to convince those of us who are skeptical that you will be part of fixing it and won't be beholden to Big Pharma."

Regarding his other priorities, Mr. Azar noted that, through his "experience helping to implement [Medicare] Part D and with my extensive knowledge of how insurance, manufacturers, pharmacy, and government programs work together, I believe I can bring the skills and experiences to the table that can help us address these issues, while still encouraging discovery so Americans have access to high-quality care."

He called for making health care "more affordable, more available, and more tailored to what individuals want and need. … Under the status quo, premiums have been skyrocketing year after year, and choices have been dwindling. We must address these challenges for those who have insurance coverage and for those who have been pushed out or left out of the insurance market by the Affordable Care Act."

Mr. Azar signaled that he will continue the push toward value-based care and will use the power of Medicare to lead the rest of the health care delivery system to follow suit.

"We can better channel the power of health information technology and leverage what is best in our programs and in the private competitive marketplace to ensure the individual patient is the center of decision making and his or her needs are being met with greater transparency and accountability."

Regarding the opioid crisis, Mr. Azar said that "we must heed President Trump's call to action and tackle the scourge of the opioid epidemic that is destroying so many individuals, families, and communities. We need aggressive prevention, education, regulatory, and enforcement efforts to stop overprescribing and overuse of these legal and illegal drugs. And we need compassionate treatment for those suffering from dependence and addiction."

Mr. Azar also was challenged on women's health issues, particularly the ability of employers to exclude health insurance coverage of contraception because of religious objections. He noted that there needs to be a balance between the medical needs of the patient and the rights of an organization to follow its conscience.

Mr. Azar also committed during the hearing to working with improving interoperability of electronic health records as well as working with physicians to reduce the associated documentation burden.

Mr. Azar's appearance before the HELP Committee was a courtesy as the Senate Finance Committee holds jurisdiction over his nomination. No confirmation hearing had been scheduled at press time.

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NOW APPROVED

FASENRA is indicated as an add-on maintenance treatment of patients 12 years or older with severe eosinophilic asthma.

POWER TO PREVENT EXACERBATIONS

WITH BETTER BREATHING AFTER THE FIRST DOSE*[1-4]

FASENRA is proven to reduce annual exacerbation rate and improve lung function in patients with severe eosinophilic asthma. Improvements in lung function were observed as early as Week 4.*[1-4]

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

*Statistical significance for FEV_1 improvement was established at end of treatment. Week 4 results were descriptive only. FASENRA demonstrated greater improvements in change from baseline in pre-bronchodilator FEV_1 compared with placebo at Week 4 (first measured time point after administration of treatment dose) that were maintained through end of treatment.[2-4]

†The pharmacodynamic response (blood eosinophil depletion) following repeat SC dosing was evaluated in asthma patients in a 12-week phase 2 trial. Patients received 1 of 3 doses of benralizumab [25 mg (n=6), 100 mg (n=6) or 200 mg (n=6) SC] or placebo (n=6) every 4 weeks for a total of 3 doses. Twenty-four hours post dosing, all benralizumab dosage groups demonstrated complete or near complete depletion of blood eosinophil levels, which was maintained throughout the dosing period.[1,5]

The relationship between the pharmacologic properties and clinical efficacy has not been established.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to benralizumab or excipients.

WARNINGS AND PRECAUTIONS

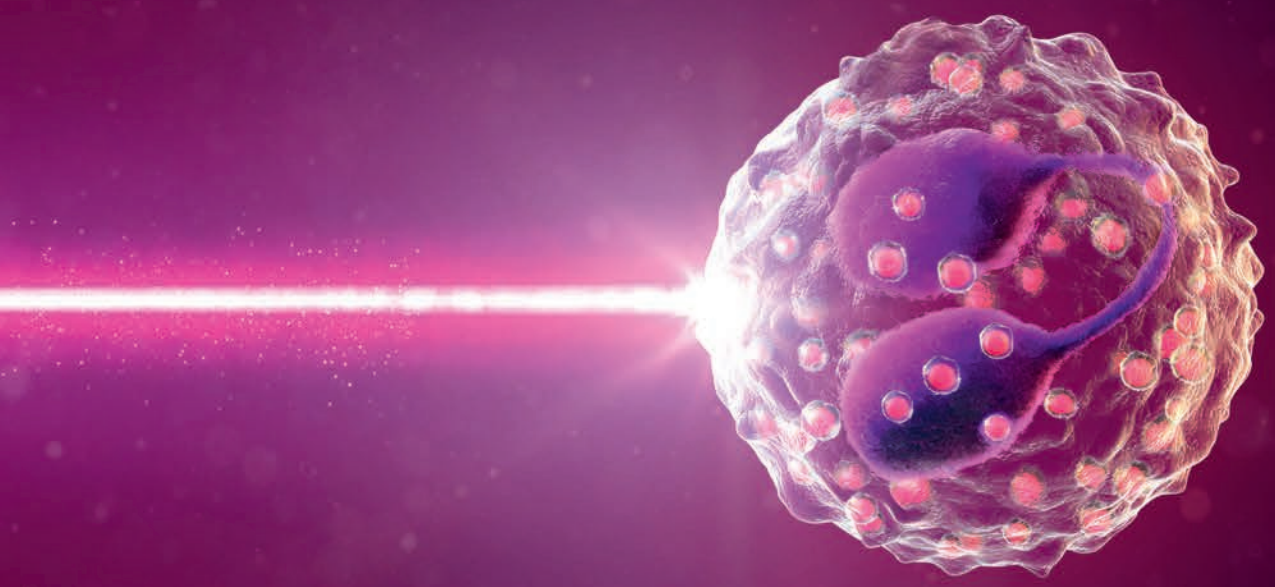
Hypersensitivity Reactions

Hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie, days). Discontinue in the event of a hypersensitivity reaction.

Acute Asthma Symptoms or Deteriorating Disease

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

- **FASENRA is the first and only biologic that provides near complete depletion of blood eosinophils in 24 hours[†1,5]**
  - **The mechanism of action of benralizumab in asthma has not been definitively established**
    - The relationship between the pharmacologic properties and clinical efficacy has not been established.
- **FASENRA is the first and only biologic for severe asthma with a prefilled syringe and Q8W maintenance dosing schedule[1]**
- **The most common adverse reactions (incidence greater than or equal to 5%) include headache and pharyngitis[1]**



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FASENRAHCP.COM

IMPORTANT SAFETY INFORMATION (cont'd)

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

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

Please see additional Important Safety Information on next page and accompanying Brief Summary of full Prescribing Information.

Fasenra™
(benralizumab) Subcutaneous Injection 30 mg
FROM THE START

STUDY DESIGNS

TRIALS 1 AND 2

Trial 1 (48-week) and Trial 2 (56-week) were 2 randomized, double-blind, parallel-group, placebo-controlled, multicenter studies comparing **FASENRA** 30 mg SC Q4W for the first 3 doses, then Q8W thereafter; benralizumab 30 mg SC Q4W, and placebo SC. A total of 1204 (Trial 1) and 1306 (Trial 2) patients aged 12-75 years old with severe asthma uncontrolled on high-dose ICS (Trial 1) and medium- to high-dose ICS (Trial 2) plus LABA with or without additional controllers were included. Patients had a history of ≥2 exacerbations requiring systemic corticosteroids or temporary increase in usual dosing in the previous year. The primary endpoint was annual exacerbation rate ratio versus placebo in patients with blood eosinophil counts of ≥300 cells/μL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV_1 and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.[2,3]

TRIAL 3

A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of **FASENRA** (30 mg SC) Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC) Q4W, and placebo (SC) Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and chronic OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/μL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.[6]

PHASE 2 STUDY

A 12-week, phase 2, randomized, double-blind, placebo-controlled, dose-increase study of benralizumab in adults with mild to moderate asthma. Patients were randomized to receive SC administration of benralizumab 25 mg (n=6), benralizumab 100 mg (n=6), benralizumab 200 mg (n=6), or placebo (n=6) Q4W for a total of 3 doses. One objective was to assess the effect of benralizumab on blood eosinophil counts and protein biomarkers. Median blood eosinophil levels at baseline were 400, 200, 120, and 200 cells/μL in the 25, 100, and 200 mg benralizumab and placebo groups, respectively.[5]

References: 1. FASENRA [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017. **2.** Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115-2127. **3.** FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128-2141. **4.** Data on File, REF-19697, AZPLP. **5.** Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21-29. **6.** Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448-2458.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) include headache and pharyngitis.

Injection site reactions (eg, pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

USE IN SPECIFIC POPULATIONS

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

INDICATION

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

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

Please see adjacent Brief Summary of full Prescribing Information on reverse side.

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

Fasenra™
(benralizumab) Subcutaneous Injection 30 mg
FROM THE START

FASENRA™ (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitations of use:

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

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

Preparation and Administration

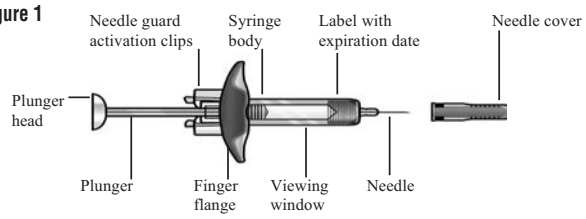
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

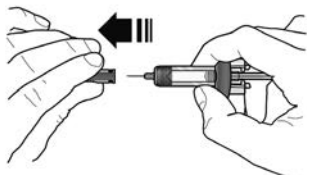
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

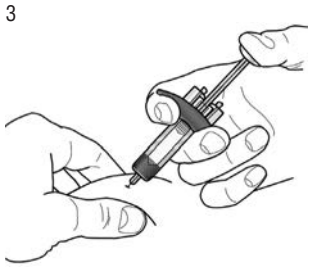
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4

Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5

After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

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

ADVERSE REACTIONS

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

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

Clinical Trials Experience

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

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14) in the full Prescribing Information]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n = 841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1) in the full Prescribing Information]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N= 822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions**	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.

** Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n = 73) or placebo (n = 75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14) in the full Prescribing Information]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

Immunogenicity

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

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the 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 benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

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

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1) in the full Prescribing Information]*. The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n= 320) were 65 and over, while 0.4% (n=9) were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare professional if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA 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 FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

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 *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

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Evidence mounts for pulmonary embolism benefit from catheter thrombolysis

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Catheter-directed thrombolysis of pulmonary embolism using an ultrasound-assisted device led to significantly better outcomes in patients hospitalized for pulmonary embolism, compared with conventional systemic thrombolytic treatment, in a propensity score–adjusted analysis of nearly 3,400 patients.

Catheter-directed thrombolysis (CDT) "represents an opportunity to locally treat pulmonary embolism with significant thrombus burden with lower bleeding complications," Abhishek Mishra, MD, said at the CHEST annual meeting. "I think we are underusing CDT," said Dr. Mishra, a cardiovascular disease physician at Guthrie Robert Packer Hospital in Sayre, Pa.

Dr. Abhishek Mishra

Dr. Victor F. Tapson

Mitchel L. Zoler/Frontline Medical News

Although one CDT device, the EKOS endovascular system that uses ultrasound to facilitate pulmonary embolism (PE) thrombolysis, received FDA approval for U.S. marketing in 2014, the trials that have compared it with systemic thrombolysis have been small, noted Dr. Mishra, and none have looked at whether CDT improves patient survival, compared with standard treatments. The largest report on CDT treatment of PE came from a single-arm, uncontrolled study with 150 patients who received ultrasound-facilitated CDT (JACC Cardiovasc Interv. 2015 Aug;8[10]:1382-92).

To better document the incremental benefit from CDT, Dr. Mishra and his associates used data collected by the Nationwide Readmissions Database during 2013 and 2014, both before and after a CDT device became available for U.S. use. From among 4,426 patients hospitalized with a primary diagnosis of PE and treated with thrombolytic therapy, they used propensity score matching to compare 2,256 patients treated with systemic thrombolysis with 1,128 matched patients treated with CDT using tissue plasminogen activator.

The analysis showed that in-hospital death was 15% in the systemic patients and 6% in the CDT group, a relative risk reduction of 63%, and 30-day readmissions occurred in 11% of the systemic patients and in 8% of those treated with CDT, a 30% relative risk reduction. Both were statistically significant differences for the study's two primary endpoints, Dr. Mishra reported at the meeting. Rates of intracerebral hemorrhage and gastrointestinal bleeds were both numerically lower with CDT, and significantly lower for gastrointestinal bleeds.

A multivariate analysis showed CDT was linked with significant relative reductions of about 60% for both in-hospital death and 30-day readmissions, compared with patients on systemic therapy. The results Dr. Mishra reported also appeared in a published report (Am J Cardiol. 2017 Nov 1;120[9]:1653-61).

These findings help buttress the case for using CDT for at least some PE patients. "The key is which patients need it," said Victor F. Tapson, MD, a pulmonologist at Cedars-Sinai Medical Center in Los Angeles.

"Patients with PE and a normal right ventricle generally don't need anything more aggressive than anticoagulation, and really sick patients with massive PE need systemic thrombolytics. Intermediate-risk patients" are best suited to CDT, but "the problem is that intermediate-risk patients are heterogeneous," Dr. Tapson said in a video interview, available at mdedg.com/chestphysician.

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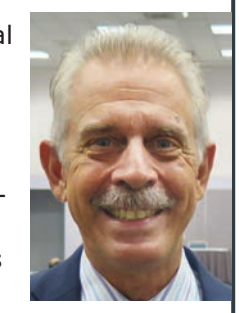
VIEW ON THE NEWS



Daniel Ouellette, MD, FCCP, comments: Recently, practitioners at my hospital have become interested in the use of catheter-directed thrombolysis to treat patients with hemodynamically significant pulmonary embolus. We developed an on-call, multidisciplinary team to make treatment decisions for patients with a significant pulmonary embolus based on institutional protocols. While we await definitive data concerning outcomes for these exciting new technologies, the team approach to this process has led to judicious and well-thought-out plans for our patients.

Infections increase risk of idiopathic VTE

BY TERRY L. KAMPS
Frontline Medical News

Infection and infection sites have been found to be associated with a significant increased risk of venous thromboembolism, according to results of a population-based, matched, case-control analysis of medical records covering the 13-year period 1988-2000.

Dr. Kevin P. Cohoon and his colleagues at the Mayo Clinic, Rochester, Minn., developed models using conditional logistic regression analysis to stratify the risk associated with specific infections and infection sites.

A total of 1,303 individuals, mean age of 65.2 years, with a first lifetime objectively diagnosed deep vein thrombosis and/or pulmonary embolism were identified and paired with 1,494 controls without venous thromboembolism (VTE), mean age of 64.9 years. The matches were based on sex, age, and an episode of medical care within 1 year of the case event date. The case population consisted of 55.6% women, compared with the control population consisting of 55.4% women.

Five hundred thirteen (39.4%) cases and 189 (12.7%) controls had an infection within the previous 92 days (odds ratio, 4.5; *P* less than .0001). Known VTE risk factors and potentially confounding variables were used in the adjusted univariate and multivariate models, as reported in the American Journal of Medicine (2017. doi: 10.1016/j.amjmed.2017.09.015).

Dr. Cohoon and his colleagues reported that univariate analysis showed "most infection sites were strongly associated with venous thromboembolism" and the adjusted multivariate model resulted in 2.4-fold (*P* less than .0001) higher odds for VTE incidence, compared with uninfected controls.

Adjusted multivariate analysis ranked the odds of VTE according to specific infections. Dr. Cohoon and his colleagues reported that this modeling showed that the "highest magnitude of risk, compared with no infection, was imparted by intra-abdominal infection (OR, 18) followed by oral infection (OR, 12), systematic blood stream infection (OR, 11), lower respiratory infection such as pneumonia (OR, 3.6), and symptomatic urinary tract infection (OR, 2.2)."

The researchers concluded that their findings may allow for further refinement of inpatient VTE risk-prediction models such as the Padua prediction score and "future studies are required to assess the utility of venous thromboembolism prophylaxis among outpatients with high venous thromboembolism risk infections."

The authors reported that they had no conflicts of interest.

Red cell age: No impact on mortality after transfusion

BY ANDREW D. BOWSER
Frontline Medical News

Critically ill patients who received transfusions of the freshest-available red cells had a mortality rate similar to that of patients who received standard-issue, oldest-available red cells, according to results from a large randomized trial.

In some earlier studies, transfusion of older red cells was linked to increased mortality for critically ill, surgical, and trauma patients. But the new results provide "strong evidence" that transfusing very fresh red cells rather than older red cells "provides no clinically meaningful benefits" in the critically ill population, reported D. James Cooper, MD, of Monash University, Melbourne, and his colleagues.

"Our results support the current international usual practice of transfusing patients with the oldest red cells available," the researchers wrote in the report on the trial, known as TRANSFUSE (Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care).

Red cells are stored up to 42 days and can undergo biochemical, structural, or metabolic changes during that time that "may cause harm," the researchers wrote. However, blood banks typically issue the oldest compatible red cell units available to them, and it's uncertain whether doing so increases mortality.

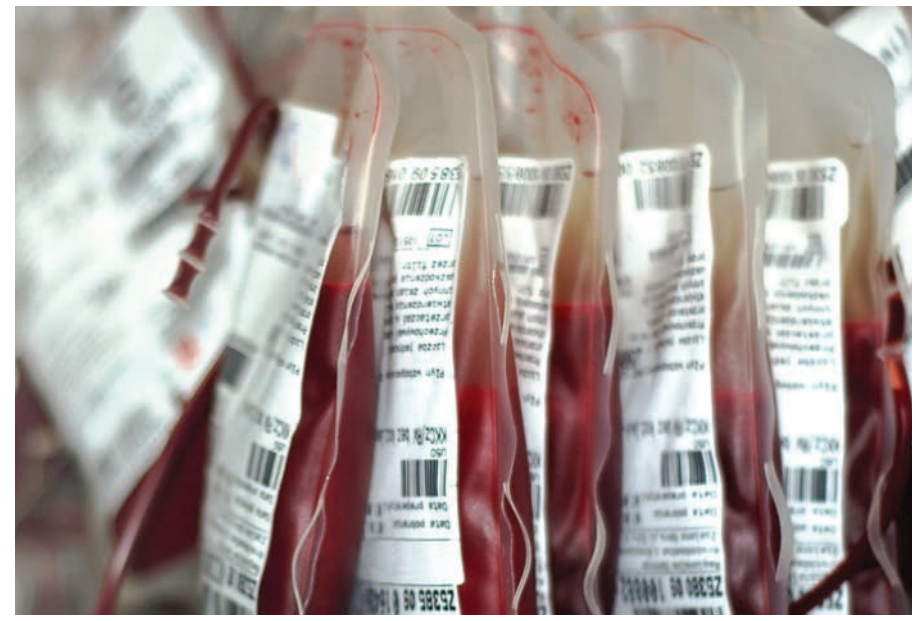
To see if the age of red cells impacted mortality, Dr. Cooper and has colleagues at 59 centers in five countries randomized 4,994 critically ill adults to receive the freshest-available or standard oldest-available red cells (N Engl J Med. 2017;377:1858-67).

At 90 days after transfusion, mortality was 24.8% in the group of patients receiving the freshest-available red cells, and 24.1% for the oldest-available group, or an absolute risk difference of just 0.7 percentage points (95% confidence interval, –1.7 to 3.1; $P = .57$).

"Among the many secondary outcomes tested, we noted a nominal difference in febrile nonhemolytic transfusion reactions that was small, and we are not sure of its clinical significance," the researchers wrote.

The average duration of red cell storage was 11.8 days versus 22.4 days for the freshest-available and oldest-available groups, respectively.

The TRANSFUSE trial is not the first to suggest that age of red blood



HEMERA/THINKSTOCK

cells does not make a difference in mortality after transfusion. There were two earlier trials, ABLE (Age of Blood Evaluation) and INFORM (Informing Fresh versus Old Red Cell Management) that came to similar conclusions. However, the ABLE trial had a small sample size, and INFORM had "limited outcome data" including a low mortality rate "suggesting low illness severity," the researchers noted.

"The lower in-hospital mortality in the ICU subgroup in the INFORM trial (13.0%) than that observed in our trial at 90 days (24.5%) is consistent with lower illness severity in the INFORM patients," they wrote.

The study was funded by organizations including the Australian National Health and Medical Research Council. Dr. Cooper reported receiving consulting fees from Eustralis Pharmaceuticals that were paid to Monash University. No other potential conflicts of interest were reported.

Alarm reductions don't improve ICU response times

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – It will take more than a reduction in alarms to address the issue of alarm fatigue in the ICU; a change in the ICU staff culture is needed, suggests new research.

"It may take years to recondition clinicians [to realize] that alarms are actionable and must get a response," Afua Kunadu, MD, said during her presentation on the study at the CHEST annual meeting. Results from prior studies had suggested that as many as 99% of clinical alarms do not result in clinical intervention, noted Dr. Kunadu, an internal medicine physician at Harlem Hospital Center in New York.

A program run at Dr. Kunadu's hospital showed that cutting back in alarm number alone did not lead to better response times to alarms. Counterintuitively, response times worsened as the total number of alarms fell. "This was a big surprise," Dr. Kunadu said. Dealing with this issue will "require a shift of focus from alarm fatigue to response time. Even though we made the alarms more actionable, the conditioning remained" that most alarms are not actionable.

She described the program, which started in the 20-bed adult ICU of Harlem Hospital Center,

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Afua Kunadu

"It may take years to recondition clinicians [to realize] that alarms are actionable and must get a response."

following a 2014 National Patient Safety Goal issued by The Joint Commission to improve the safety of clinical alarm systems by reducing unneeded alarms and alarm fatigue. The Harlem Hospital task force that ran the program began with an audit of alarms that went off in the ICU and used the results to identify the three most common alarms: bedside cardiac monitors, infusion pumps, and mechanical ventilators. The task force arranged to reset the default settings on these devices to decrease alarm frequency and boost the clinical importance of each alarm that still sounded. Concurrently, they ran educational sessions about the new alarm thresholds, the anticipated drop in alarm number, and the increased urgency to respond to the remaining alarms very quickly for the ICU staff.

The raised thresholds effectively cut the number of alarms. The average number of alarms per patient per hour fell from 4.5 at baseline during September 2016 to about 2 after 1 month, during December 2016. Then the rate further declined to reach a steady nadir that stayed at about 1.3 alarms per patient per hour 4 months into the program.

But timely responses, measured as the percentage of alarm responses occurring within 60 seconds after the alarm went off, fell from 60% at 1 month into the program down to 12% after 4 months, Dr. Kunadu reported.

She had no disclosures.

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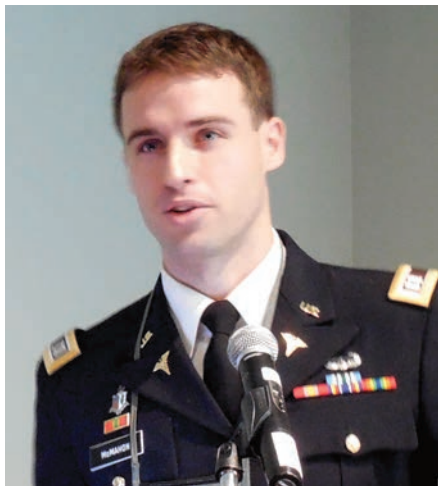
Acute kidney injury linked with doubled inpatient VTEs

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Hospitalized patients with acute kidney injury had more than double the inpatient rate of venous thromboembolism than did patients without acute kidney injury in a prospective, observational study of more than 6,000 hospitalized U.S. soldiers.



MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Michael McMahon

"I think this should lower our threshold for investigating [possible cases of] venous thromboembolism in patients with acute kidney injury," Michael McMahon, MD, said at the CHEST annual meeting. Acute kidney injury (AKI) "may require new prophylactic or diagnostic strategies" to prevent in-hospital venous thromboembolism (VTE) or to detect it early, said Dr. McMahon, a pulmonologist and critical care medicine physician at Walter Reed National Military Medical Center in Bethesda, Md.

He offered four possible mechanisms to explain a link between AKI and VTE:

- Patients with AKI are in a hypercoagulable state.
- AKI alters the pharmacodynamics or pharmacokinetics of VTE prophylactic treatments.
- AKI is a marker of an illness that causes VTE.
- VTE leads to an increased rate of AKI rather than the other way around.

Dr. McMahon's analysis also revealed that two other clinical conditions that are generally believed to raise VTE risk – obesity and impaired overall renal function identified with stagnant measures – did not correspond with a significantly elevated VTE rate in this study.

The data came from 6,552 adults hospitalized for at least 2 days at Walter Reed between September 2009 and March 2011. The study excluded patients with VTE at the time of admission and also those who had been treated with an anticoagulant at the time of admission. The patients averaged 55 years of age and were hospitalized for a median of 4 days. About 22% of patients received VTE prophylaxis with unfractionated heparin, about 41% received prophylaxis with low-molecular-weight heparin, and about 39% received no VTE prophylaxis (percentages total 102%

because of rounding).

About 16% of the patients had been diagnosed with AKI at the time of admission, and an additional 8% developed AKI while hospitalized, defined as an increase in serum creatinine during hospitalization of at least 50% above baseline levels or an increase of more than 0.3 mg/dL above the level at time of admission. During hospitalization, 160 patients (2%) developed a new-onset VTE.

In an analysis that adjusted for baseline differences in type of surgery, body mass index, sex, age, and prior hospitalizations during the prior 90 days, the results showed that patients with preexisting or new-onset AKI had a 2.2-fold higher rate of VTE, compared with patients without AKI, and this difference was statistically significant, Dr. McMahon reported.

The analysis also showed a significant 62% relatively higher rate of VTE among soldiers hospitalized for a deployment-related event, as well as a significant 63% relatively lower VTE rate among patients not receiving medical prophylaxis, compared with patients receiving an anticoagulant. Dr. McMahon suggested that this lower rate of VTEs among patients not on prophylaxis reflected success in identifying which patients had an increased risk for VTE and hence received prophylaxis.

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Pulmonary hypertension treatment gets under the skin

BY HEIDI SPLETE
Frontline Medical News

FROM CHEST ▪ Pulmonary arterial hypertension (PAH) patients with moderate, stable disease can benefit from an implantable drug delivery system, based on data from a review of 60 adults with successful implantations. The findings were published in the December issue of CHEST.

"A fully implanted system offers patients the hope of returning to more normal activities such as bathing, swimming, and reduced risk of infections from externalized central venous catheter contamination or reduced subcutaneous pain from subcutaneous infusion," wrote Aaron B. Waxman, MD, PhD, of Brigham and Women's Hospital, Boston, and his colleagues (Chest. 2017 June 3. doi: 10.1016/j.chest.2017.04.188).

In the DelIVery Trial, clinicians at 10 locations in the United States placed a fully implantable delivery system in adults aged 18 years and older with stable PAH who were previously receiving treprostinil via an external pump at an average dose of 71 ng/kg per minute.

"A fully implanted system offers patients the hope of returning to more normal activities such as bathing, swimming, and reduced risk of infections from externalized central venous catheter contamination or reduced subcutaneous pain from subcutaneous infusion."

All 60 patients were successfully implanted with a system consisting of a drug infusion pump placed in an abdominal pocket and an intravascular catheter linking the implanted pump to the superior vena cava.

"The location of the pump pocket was determined in partnership with the patient and was based on consideration of clothing styles, belt line and subcutaneous fat depth," the researchers noted.

Procedure-related complications deemed clinically significant included one atrial fibrillation, two incidences of pneumothorax, two infections unrelated to catheter placement, and three catheter dislocations (two in the same patient). The most common patient complaints were expected implant site pain in 83% and bruising in 17%.

The findings were limited by the small number of patients, but the researchers identified several factors that contributed to the success of the procedure, including selecting patients who have shown response to treprostinil and are motivated to comply with pump refill visits, performing the procedure at centers with a high volume of PAH patients,

Continued on following page

Heart transplantation: Preop LVAD erases adverse impact of pulmonary hypertension

BY BRUCE JANCIN
Frontline Medical News

COLORADO SPRINGS – Reconsideration of the role of pulmonary hypertension in heart transplant outcomes is appropriate in the emerging era of the use of left ventricular assist devices (LVADs) as a bridge to transplant, according to Ann C. Gaffey, MD, of the University of Pennsylvania, Philadelphia.

"Pulmonary hypertension secondary to congestive heart failure more than likely can be reversed to the values acceptable for heart transplant by the use of an LVAD. For bridge-to-transplant patients, pretransplant pulmonary hypertension does not affect recipient outcomes post transplantation," she said at the annual meeting of the Western Thoracic Surgical Association.

"Pulmonary hypertension secondary to congestive heart failure more than likely can be reversed to the values acceptable for heart transplant by the use of an LVAD."

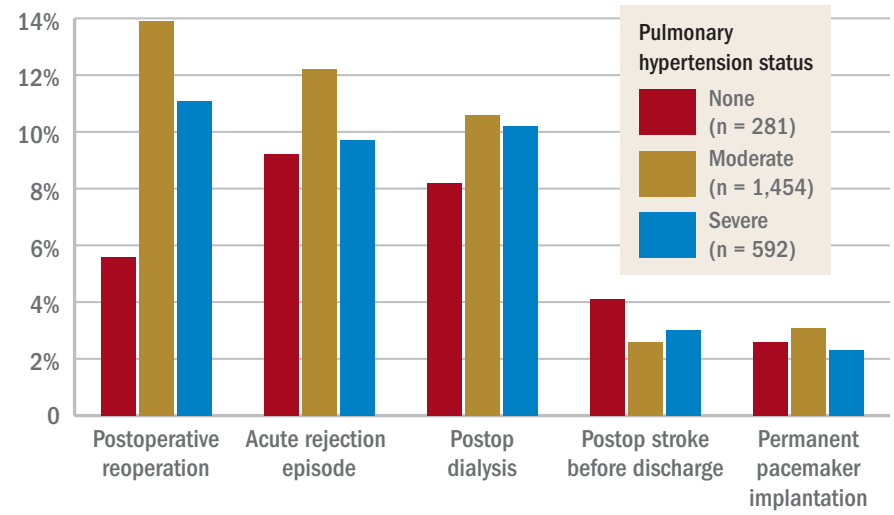
Historically, pulmonary hypertension (PH) has been associated with early mortality due to right heart failure and poor transplant survival. An influential report of more than a decade ago by the National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Heart Failure concluded that patients with severe PH as defined by more than 3 Wood units plus poor right ventricular function have a 2-year survival of less than 50% (Circulation. 2006 Oct;114[17]:1883-91).

Vasodilators are prescribed in an effort to reduce PH; however, 40% of patients with PH are unresponsive to the medications and have therefore been excluded from consideration as potential candidates for a donor heart.

But the growing use of LVADs as a bridge to transplant has changed all that, Dr. Gaffey said. As supporting evidence, she presented a retrospective analysis of the United Network for Organ Sharing database on adult heart transplants from mid-2004 through the end of 2014.

The review turned up 3,951 heart transplant recipients who had been bridged to transplant with an LVAD. Dr. Gaffey and her coinvestigators divided them into three groups: 281 patients without pretransplant PH; 1,454 with moderate PH as defined by 1-3 Wood units; and 592 with severe PH and more than 3 Wood units.

In-hospital outcomes after LVAD bridge to transplant



Notes: No significant between-group differences were found. Based on data from the United Network for Organ Sharing for heart transplants from mid-2004 through the end of 2014.

Source: Dr. Gaffey

The three groups didn't differ in terms of age, sex, wait-list time, or the prevalence of diabetes or renal, liver, or cerebrovascular disease. Nor did their donors differ in age, sex, left ventricular function, or allograft ischemic time.

Key in-hospital outcomes were similar between the groups with no, mild, and severe PH.

Moreover, there was no between-group difference in the rate of rejection at 1 year. Five-year survival rates were closely similar in the three groups, in the mid-70% range.

Audience member Nahush A. Mokadam, MD, rose to praise Dr. Gaffey's report.

"This is a great and important study. I think as a group we have been too conservative with pulmonary hypertension, so thank you for shining a good light on it," said Dr. Mokadam of the University of Washington, Seattle.

Dr. Gaffey reported having no financial conflicts regarding the study, which was conducted free of commercial support.

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VIEW ON THE NEWS

Implant may improve quality of life for stable PAH patients

The development of an implantable therapy for pulmonary hypertension could expand the use of treprostinil, a demonstrated effective treatment for PAH that has been limited in its use because of a range of side effects when given intravenously, orally, subcutaneously, or by inhalation, Joel A. Wirth, MD, and Harold I. Palevsky, MD, FCCP, wrote in an editorial.

The use of an intravenous pump and catheter infusion system for stable PAH patients could help them return more quickly to normal activities and curb the risk of catheter-related infections, they said. "Having the potential to remove some of the burden and risk incumbent with an external delivery system may reduce several of the overall barriers to continuous intravenous prostanoid acceptance by both patients and providers," they noted (Chest. 2017 Dec 6. doi: 10.1016/j.chest.2017.07.006).

Clinicians must be educated to perform the implant procedure itself, and care centers must be trained in identifying patient management issues and refilling the pump reservoir as needed, Dr. Wirth and Dr. Palevsky emphasized. Patients must be educated in what to expect, including how to monitor the pump and track the need for refills, they said. Although the pump is not appropriate for patients with severe PAH, "a planned staged approach of transitioning PAH patients from IV therapy to a less complex system could lend itself to employing prostanoid use earlier and for less severely affected PAH patients," they said.

Dr. Wirth is affiliated with Tufts University, Boston. Dr. Palevsky is affiliated with the University of Pennsylvania, Philadelphia. Both Dr. Wirth and Dr. Palevsky disclosed serving as consultants and as principal investigators for United Therapeutics.

Continued from previous page

keeping the procedure consistent for each patient, and using the same implant team in each case. "The implant procedure was successfully performed with a low complication rate by clinicians with a diverse range of specialty training," the researchers added.

Patients reported satisfaction with the implant system at 6 weeks and 6 months, and said they spent an average of 75% less time managing their delivery system, according to previously published data on the patients' perspective (CHEST 2016;150[1]:27-34).

Medtronic sponsored the study. The lead author, Dr. Waxman, reported not having any financial conflicts to disclose; several coauthors reported relationships with companies including Medtronic, Actelion, Bayer, Gilead, Merck, and United Therapeutics.

RELEASE THE POTENTIAL OF NUCALA

The first subcutaneous anti-interleukin 5 (IL-5) targeted therapy for severe asthma with an eosinophilic phenotype

Indication

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 treatment of other eosinophilic conditions or for the relief of acute bronchospasm or status asthmaticus.

Important Safety Information

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions (eg, 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 in subjects treated with NUCALA, compared with none in placebo. Consider varicella vaccination, if medically appropriate, prior to starting therapy with NUCALA.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids 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%).

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.

Benefits of NUCALA:

- **SIGNIFICANTLY REDUCED EXACERBATIONS* BY 53%** in the MENSA trial (NUCALA: 0.83/year vs placebo: 1.74/year; *P*<0.001)[1]
- **SIGNIFICANTLY REDUCED DAILY OCS DOSE WHILE MAINTAINING ASTHMA CONTROL,** in the SIRIUS trial (vs placebo; *P*=0.008)[2]
- **IMPROVED QUALITY OF LIFE** in the MENSA trial (SGRQ responder rate: NUCALA, 71%, vs placebo, 55%; odds ratio: 2.1; 95% CI: 1.3, 3.2)†

  Statistical hierarchy was not met; endpoint is exploratory and results are descriptive only.[3]

MENSA (Trial 2)[1]: 32-week study comparing treatment with NUCALA or placebo, added to regular treatment with high-dose ICS and at least 1 other controller with or without OCS, in 576 patients with severe asthma with an eosinophilic phenotype.‡
Primary endpoint: Frequency of exacerbations.

SIRIUS (Trial 3)[2]: 24-week study comparing treatment with NUCALA or placebo in 135 patients with severe asthma with an eosinophilic phenotype‡ who required at least 5 mg to 35 mg of prednisone equivalent per day in addition to regular use of high-dose ICS plus an additional controller.
Primary endpoint: Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control.

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

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

†The SGRQ is a validated measure of health impairment for chronic respiratory diseases and is able to address the impact asthma has on a patient's quality of life. Response was defined as a reduction in score of 4 points or more.[4]

‡Identified by blood eosinophil counts ≥150 cells/μL at initiation of treatment (within 6 weeks of dosing) or ≥300 cells/μL in the past 12 months.

Visit **NUCALAHCP.COM** to learn more

Important Safety Information (cont'd)

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

References: 1. 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. **2.** Bel EH, Wenzel SE, Thompson PJ, et al; for the SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197. **3.** Data on file, GSK. **4.** Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J*. 2002;19(3):398-404.

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

Nucala®
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA®
(mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

NUCALA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. *[See Clinical Studies (14) of full prescribing information.]*

Limitations of Use

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

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

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with none in placebo *[see Adverse Reactions (6.1)]*. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

5.4 Reduction of Corticosteroid Dosage

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

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)]*

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.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (Trials 1 and 2), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (Trial 3). All subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14) of full prescribing information]*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.2 Immunogenicity

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

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

6.3 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 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 from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimesters of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) of 100 mg SC *[see Data]*.

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

Clinical Considerations

Disease-Associated Maternal and/or 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 30 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to day 178 postpartum. Levels of mepolizumab in milk were less than or equal to 0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine 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.

8.4 Pediatric Use

The safety and efficacy in pediatric patients younger than 12 years have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the phase 3 studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had a history of 2 or more exacerbations in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) with or without oral corticosteroids and had blood eosinophils of greater than or equal to 150 cells/mcL at screening or greater than or equal to 300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14) of full prescribing information.]* Subjects had a reduction in the rate of exacerbations

8.4 Pediatric Use (cont'd)
that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the phase 3 studies *[see Adverse Reactions (6.1)]*.

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

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 treated with mepolizumab for 6 months at IV doses up to 100 mg/kg once every 4 weeks (approximately 70 times the MRHD on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice treated with an analogous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week.

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 varicella vaccination should be considered before starting treatment with NUCALA.

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

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

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Tuberculosis transmission stemmed

BY ELI ZIMMERMAN
Frontline Medical News

SAN DIEGO – Using an on-site multidisciplinary team to approach patients who are unwilling to receive tuberculosis treatment can improve patient cooperation, according to a case study presented at ID Week 2017, an infectious disease meeting.

Such public health interventions may be able to improve disease control and interrupt the transmission cycle among patients who are not adhering to treatment, according to Aisha Haynie, MD, MPA.

The first patient Dr. Haynie and her colleagues interacted with as a team was a young female adult diagnosed with active TB, who had been going back and forth from the hospital over the course of 10 months, according to Dr. Haynie.

"We started the patient on treatment and she actually decided to move into a motel," said Dr. Haynie. "After that, she moved back into the family home and said she wasn't having any contact [with residents], which we didn't really believe."

While the patient did reluctantly give Dr. Haynie and her team a list of five family members to test, the patient told Dr. Haynie that she and her team were not allowed into the patient's home.

When the five members were tested, the new patients showed similar signs of reluctance and mistrust of the health system.

"The family members came to our clinic and two of them were TB positive," recounted Dr. Haynie. "So they came back, but while they were sitting in the waiting room, they signed papers and they left."

Despite continuous attempts to reach the family and address the growing concern from health professionals of the danger of TB transmission to other members of the family, the patients continued not to adhere to procedures beyond pharmaceutical intervention.

In an attempt to directly contact the patient's family, Dr. Haynie led a team consisting of a local health authority physician, a TB nurse practitioner, a TB contact analyst, a nurse case manager, a county attorney, and an interpreter for unscheduled visits to family members individually.

"We had specific requests [including] keeping appointments, getting labs, and we added a deadline," said Dr. Haynie, chief of disease control and medical epidemiology for Harris County (Tex.) Public Health & Environmental Services. "By the next Friday [we told them that] we were filing court papers with or without the information and we [would] be contacting child protective services as well."

Following the intervention, the patient and her family adhered to testing procedures. This revealed an infant with active TB and 8 other family members with TB infection. Isolation breaches were also discovered. Most importantly, the TB transmission cycle was interrupted, according to Dr. Haynie.

A key aspect of the team's successful approach was to address cultural and economic barriers that hindered successful interaction with the family and to correct TB misconceptions in order for a trusting relationship to develop.

The investigators developed this intervention in Harris County, which at 4.3 million residents is the 3rd most populous U.S. county and has reported a TB rate of 7.6 cases per 100,000, or approximately double that of the U.S. average, according to Dr. Haynie. Of those cases in Harris County, 73% are foreign-born, compared with the average rate of 59% in Texas.

Dr. Haynie and fellow investigators asserted that part of the reason patients were so reluctant to receive treatment from the Harris County Public Health department was a combination of mistrust in the system and a number of false ideas patients have regarding TB, a sign of further educational tools being needed.

Since the first use of the intervention, Dr. Haynie and her team have implemented this approach with other non-adherent patients with relative success.

"This is something that we now do and we have not been back to court [to enforce compliance] since," said Dr. Haynie.

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ARDS incidence is declining; is it a preventable syndrome?

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – The incidence of acute respiratory distress syndrome (ARDS) is on the decline, according to a retrospective, population-based cohort study conducted at the Mayo Clinic in Rochester, Minn.

"This is very promising data in combating this syndrome," said Augustin Joseph of the Mayo Clinic, and "it suggests that ARDS may in part be a completely preventable disease."

This study was inspired by a previous effort by Guangxi Li et al. who conducted a population-based cohort study on trends in ARDS using data from the Olmsted County (Minn.) Epidemiology Project from 2001 to 2008 (Am J Respir Crit Care Med. 2011;183:59-66). At that time, a steady and significant decline in ARDS incidence was noted, attributable to a reduced incidence of hospital-acquired ARDS. "We attributed this to improvements in hospital practices and management of ARDS and all the research that's been done over the past 2 decades," Mr. Joseph said at the CHEST annual meeting.

To see if ARDS incidence has continued to decline, Mr. Joseph's group studied all patients admitted during 2009-2014 to the Mayo Clinic's ICU, the only facility in the county that cares for ARDS patients. From 82,388 ICU admissions, they identified 505 patients with ARDS according to the Berlin definition of ARDS developed in 2012.

The number of annual cases dropped from 108 in 2009 to 59 in 2014, and the incidence steadily declined from 74.5 cases per 100,000 in 2009 to 39.3 per 100,000 in 2014.

Median age was 67 years in 2009 and 62 years in 2014. Hospital mortality ranged from 15% to 26% during the study period, while hospital length of stay ranged from 8 to 15 days, with no clear decline in either.

While the earlier study used the American-European Consensus Conference (AECC) definition of ARDS, Mr. Joseph and his colleagues diagnosed ARDS according to the Berlin definition.

RA ups risk of hospitalizations from COPD

BY ANDREW D. BOWSER
Frontline Medical News

Individuals with rheumatoid arthritis (RA) had an increased risk of hospitalizations from chronic obstructive pulmonary disease (COPD) when compared with the general population in a Canadian retrospective, population-based cohort study.

The risk of COPD hospitalizations was 47% higher in individuals with RA. "This finding emphasizes the need to control inflammation in rheumatoid arthritis, not only to prevent joint damage, but also to prevent complications of systemic inflammation, including the development of comorbidities such as cardiovascular diseases and COPD," wrote Diane Lacaille, MD, of the University of British Columbia, Vancouver, and her coauthors (Arthritis Care Res. 2017 Oct 19. doi: 10.1002/acr.23410).

Several previous studies have suggested a link between COPD and inflammation, Dr. Lacaille and her colleagues said. Accordingly, they sought to evaluate the risk of COPD hospitalizations in a cohort of 24,625 individuals with RA as compared with 25,396 general population controls randomly selected and matched based on age, sex, and index year. Most subjects in the analysis were female, and the mean age at onset of RA was 57.2 years.

The investigators reported an increased incidence of COPD in individuals with RA, compared with controls, based on an incident rate ratio (IRR) of 1.58 (95% confidence interval, 1.34-1.87) that dropped to 1.47 (95% CI, 1.24-1.74) after adjustment for potential confounders, including comorbidities and health services usage at baseline. The overall incidence rate for COPD was 2.07 per 1,000 patient-years for RA patients and 1.31 per 1,000 patient-years for controls.

When the model was stratified based on sex, COPD hospitalization risk was significantly increased in women (adjusted hazard ratio [HR], 1.61; 95% CI, 1.30-1.98), but not in men (adjusted HR, 1.25; 95% CI, 0.95-1.66), they said.

Data were not available on smoking, the main COPD risk factor, for the patients in this study; however, the increased risk of COPD hospitalizations in the RA group remained significant after modeling for smoking, according to the investigators.

Combined, these results have "notable implications for the clinical care of RA and COPD," Dr. Lacaille and her coinvestigators said.

Both clinicians and people living with RA "should be aware of the increased risk of developing COPD and be vigilant in watching for early symptoms of COPD, so that appropriate diagnostic tests can be administered at the onset of early symptoms," they wrote. "Early detection of COPD is essential so that effective treatments can be initiated before irreversible damage to the lungs occurs, to improve long-term outcomes."

These findings strengthen the conclusions of two previous cross-sectional studies showing an association between RA and COPD prevalence, according to the investigators. In one study, RA patients in Israel who were receiving disease-modifying antirheumatic drugs had double the prevalence of COPD, compared with general population controls, according to authors of that study (Immunol Res. 2013;56[2-3]:261-6). Similarly, U.K. investigators compared 421 RA patients against controls and reported a twofold increase in obstructive pattern on screening spirometry in the RA group (Ann Rheum Dis. 2013;72:1517-23).

The current study from Dr. Lacaille and her coinvestigators was supported by funding from the Canadian Institute for Health Research. The authors reported that they had no financial disclosures, conflicts of interest, or benefits from commercial sources.

Omalizumab helps asthma COPD overlap patients

BY DEBRA L. BECK
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – Omalizumab (Xolair, Genentech) decreased asthma exacerbations and improved symptom control to a similar extent in patients with asthma chronic obstructive pulmonary disease (ACO) overlap as seen in patients with asthma but no COPD, in a study presented at the CHEST annual meeting.

While patients with COPD typically experience annual declines in lung function, at least some of the ACO patients in this study, which included one of the largest observational cohorts to date of patients with ACO, showed preserved lung function after 48 weeks of omalizumab treatment.

"These data deal with a topic that we scratch our heads about all the time – the asthma COPD overlap. … Few of our therapies for asthma have been studied in this patient population," said Nicola Hanania, MD, FCCP, of Baylor College of Medicine in Houston. "We believe that about 16% of patients with asthma or COPD have ACO," he added.

Dr. Hanania presented data from the "real-world" PROSPERO (Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab), which unlike many asthma studies, did not exclude patients with comorbid COPD. PROSPERO was a prospective, multicenter, observational, 48-week study of patients (n = 806) who were 12 years of age and older who were initiating omalizumab treatment for moderate to severe allergic asthma. Asthma control was assessed monthly using the Asthma Control Test (ACT).

DEBRA BECK/FRONTLINE MEDICAL NEWS

Dr. Nicola Hanania

Participants were identified as having ACO based on two approaches: a positive medical history of asthma and COPD; or A medical history of asthma (but not COPD), at least a 10-pack per year smoking history, and a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) of less than 0.7. From the 728 study participants included in this secondary analysis, 56 were classified as ACO according to the first definition (ACO cohort A) and 59 according to the second (ACO cohort B). Thirty-seven patients fell into both groups.

"All groups had a reduction in their exacerbation rates through 12 months, and it didn't differ whether they had ACO in cohort A or cohort B, or no ACO," Dr. Hanania reported. Specifically, asthma exacerbations numbers were reduced from baseline levels though month 12, from 3 or more exacerbations in both ACO and non ACO groups to 1.1 or less.

Additionally, all three groups showed clinically meaningful improvements in their ACT scores, with mean improvements of 4.1, 4.7, and 4.4 units for ACO cohort A, ACO cohort B, and non-ACO patients, respectively.

Postbronchodilator FEV_1 at study end was improved by 36 mL in ACO cohort A and by 23 mL in the non-ACO cohort. But a 14 mL reduction in postbronchodilator FEV_1 was noted in ACO cohort B, "a reminder that the cohort B population was those patients with fixed airway obstruction and smoking history," said Dr. Hanania.

Mean age in the non-ACO population was 50 years, rising to 57.6 years in ACO cohort A and 55 years in ACO cohort B. All three groups had three or more asthma exacerbations in the 12 months before starting omalizumab, and all groups had mean ACT scores of less than 15 at baseline, indicating that they were all symptomatic.

Adverse events were consistent with the known safety profile of omalizumab.

"The significance of this study [is that] it's one of the largest ACO cohorts that we know of and I think it encourages all of us to look at or re-visit both COPD therapies and asthma therapies in populations [not included] in clinical trials because in real life, these are the patients we see … and we don't have evidence," Dr. Hanania said.

Dr. Hanania reported receiving research support from Roche/Genentech, among other companies. Three of the investigators are employees of Genentech, the study's sponsor.

For appropriate patients with DVT/PE

Choose ELIQUIS from the **START**

DVT: deep vein thrombosis; PE: pulmonary embolism.

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.

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.

Eliquis®
(apixaban) tablets 5mg 2.5mg

ELIQUIS for initial DVT/PE treatment*—

And for appropriate patients, continue on a low dose† to reduce the risk of recurrent DVT/PE following initial therapy[1]

To learn more about ELIQUIS, visit

hcp.eliquis.com

*Initial therapy: 10 mg, orally twice daily for the first 7 days. After 7 days, 5 mg orally twice daily.
†Extended therapy: 2.5 mg, orally twice daily. **Please see full dosing information in the Prescribing Information.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

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

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require 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

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, 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.

Reference: 1. ELIQUIS® Package Insert. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY.

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

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

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, 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).

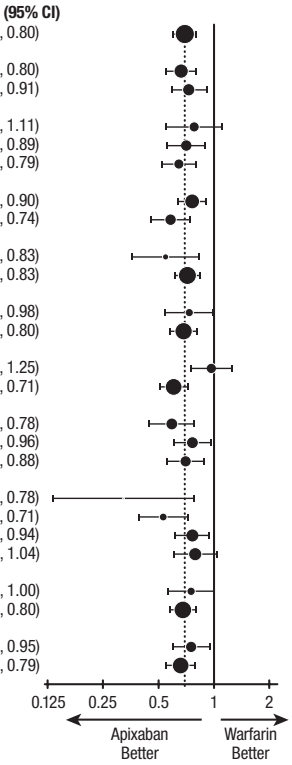
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).

§ 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 pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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.

Strong Dual Inhibitors of CYP3A4 and P-gp

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

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[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 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 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 ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) 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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Tezacaftor-ivacaftor combo shows promise in CF

BY BIANCA NOGRADY
Frontline Medical News

A new drug that targets the cystic fibrosis transmembrane conductance regulator protein could significantly improve lung function and other symptoms in patients with cystic fibrosis.

In a phase 3 double-blind, placebo-controlled crossover trial, researchers examined the effects of tezacaftor – a cystic fibrosis transmembrane conductance regulator (CFTR) corrector – in combination with the CFTR potentiator ivacaftor, compared with ivacaftor alone or placebo.

According to a paper published in the New England Journal of Medicine, the 248 cystic fibrosis patients enrolled in the study were heterozygous for the CFTR Phe508del mutation, which can be associated with more severe disease, and a second CFTR mutation that is called a "residual function" mutation. Approximately 5% of the patients with cystic fibrosis exhibit residual CFTR activity in epithelial cells, for example. Patients with one residual function mutation and a second CFTR mutation have a reduced life expectancy but the symptoms have a slower progression.

"The addition of the CFTR corrector tezacaftor was hypothesized to enhance clinical benefit in patients with these mutations by increasing overall CFTR function," wrote Dr. Steven M. Rowe of the division of pulmonary, allergy, and critical care medicine at the University of Alabama at Birmingham and his coauthors. "This combination treatment is particularly important for restoring activity to those carrying two copies of the Phe508del CFTR mutation, as shown for the approved corrector-potentiator combination lumacaftor-ivacaftor, and may provide benefit to patients with other CFTR mutations."

After two 8-week treatment periods in which patients were randomized to two of the three regimens, separated by an 8-week washout period, researchers saw significant improvements in predicted forced expiratory volume in 1 second (FEV_1), both with tezacaftor-ivacaftor and ivacaftor alone, compared with placebo (N Engl J Med. 2017 Nov 23;377:2024-35. doi: 10.1056/NEJMoa1709847).

From baseline to the average of week 4 and 8, the combination of tezacaftor-ivacaftor was associated with a 6.8-percentage-point absolute change, and there was a 4.7-percentage-point improvement with ivacaftor alone, compared with placebo. The difference between the tezacaftor-ivacaftor combination and ivacaftor monotherapy was also statistically significant in favor of the combination treatment.

Researchers also saw significant improvements in the secondary endpoint of absolute change in the Cystic Fibrosis Questionnaire–Revised score; the combination treatment was associated with an 11.1 point improvement compared with placebo, and monotherapy achieved a 9.7-point improvement. In the combination therapy group, 65% of patients achieved a clinically important difference of 4 points or greater, compared with 58% of patients in the monotherapy group and 33% of patients in the placebo group.

"These findings confirm the benefits of potentiator therapy in patients with residual CFTR function mutations and the added benefit conferred by corrector-potentiator combination therapy in this population," the authors wrote.

The investigators also saw a lower rate of pulmonary exacerbations in the combined therapy group, but this did not reach statistical significance.

The rate of adverse events was similar across all three groups. Most were considered mild or moderate in severity and were largely clinical manifestations of cystic fibrosis.

Vertex Pharmaceuticals, which manufactures tezacaftor and ivacaftor, funded the study. Twelve of the 13 authors reported receiving various kinds of support from Vertex, including personal fees, grant support, and nonfinancial support. Several authors reported ties to other industry sources.

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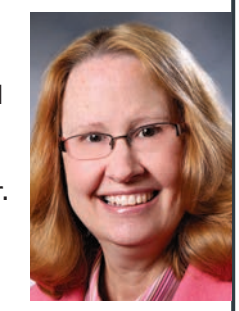
Susan Millard, MD, FCCP, comments: This NEJM article came out with a companion article reporting phase 3 tezacaftor-ivacaftor results in homozygous CFTR Phe508del patients. Tezacaftor is a CFTR corrector developed by a company that has another corrector on the market, called lumacaftor. Lumacaftor is formulated with ivacaftor and available in the United States for patients age 6 and above who have two copies of Phe508del. It is exciting that another combination therapy has been developed that appears to be very effective and can be used for a second group of patients. This era of personalized medicine is extremely exciting, and we look forward to future therapies for all CFTR mutations.



Expanded testing improves respiratory pathogen detection

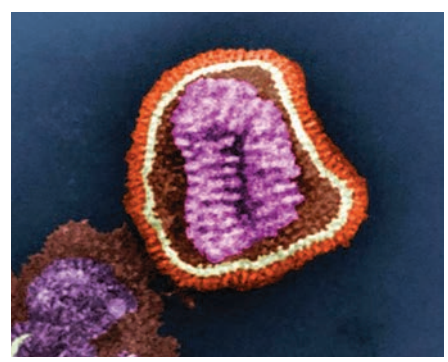
BY ELI ZIMMERMAN
Frontline Medical News

SAN DIEGO – Systematic testing of acute respiratory illness patients can increase the likelihood of finding relevant pathogens, according to a study presented at an annual scientific meeting on infectious diseases.

Currently, hospitals conduct either nonroutine assessments or rely heavily on clinical laboratory testing among severe acute respiratory illness patients, which can lead to missing clinically key viruses.

"Detections of some potentially relevant viruses, such as air influenza viruses and human metapneumovirus were often not detected in hospital testing," said presenter Andrea Steffens, an epidemiologist at the Centers for Disease Control and Prevention.

Systematic testing expands on tests ordered and carried out at hospitals, expanding on them by testing for influenza, respiratory syncytial virus (RSV), human metapneumovirus, rhinovirus and enterovirus, adenovirus, coronavirus, and parainfluenza viruses 1-4. To test the efficacy of systematic testing, investigators studied 2,216 severe acute respiratory illness patients hospitalized in one of three hospitals in Minnesota during September 2015-August 2016. Patients were predominantly younger than 5 years old (57%) and had one or more chronic medical condition (63%).



CYNTHIA GOLDSMITH/CDC

This negative-stained transmission electron micrograph (TEM) depicts the ultrastructural details of an influenza virus particle, or "virion."

Detection of at least one virus increased from 1,062 patients (48%) to 1,600 patients (72%) when comparing clinically ordered tests against expanded, systematic RT-PCR testing conducted through the Minnesota Health Department (MDH).

By patient age, viral detection increased by 27%, 24%, 18%, and 21% for patients aged younger than 5 years, 5-17 years, 18-64 years, and 65 years and older, respectively. Except for influenza viruses and RSV, the proportions of viruses identified, regardless of age, were all lower in hospital testing, compared with MDH testing.

"RSV targeting was almost systematic among children less than 5 years, but [accounted for] only 28% of RSV detection," said Dr. Steffens in her presentation. "A smaller proportion of other respiratory viruses, including the human metapneumovirus, were detected at the hospital, and this was especially true for adults."

Patients with rhinovirus and enterovirus saw a difference between hospital and expanded testing, increasing from a little over 300 patients detected, to nearly 800 patients.

"Patients admitted to the ICU were less likely to have a pathogen detection than those not admitted to the ICU, and those with one or more chronic medical conditions had lower viral detection than those without," Dr. Steffens said. "While testing at MDH did increase the percent of patients in each category, trends remained consistent and significant."

Since testing information was only collected for patients with positive test results at the hospital, investigators were not able to compare testing practices between patients with and without viruses.

The presenters reported no relevant financial disclosures.

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Testing for latent tuberculosis infection

BY NEIL SKOLNIK, MD, AND MATHEW CLARK, MD
Frontline Medical News

While cases of active tuberculosis are relatively rare in the United States, TB is a major cause of morbidity and mortality worldwide. In the United States, there are an estimated 11 million individuals who have latent TB infection (LTBI). Without prophylactic treatment, somewhere between 4%-6% of individuals with LTBI will develop active disease during their lifetimes; roughly half of these cases will occur within a few years of the initial infection. Treatment of LTBI reduces – but does not eliminate – the risk for active disease, decreasing the consequences of active disease for the patient and the risk of transmitting infection to others.

Guidelines from the American Thoracic Society, the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention have been issued with new recommendations for optimal testing strategies for detecting LTBI. The recommended strategies are based on two criteria: the risk of being infected with TB and, in those with LTBI, the risk of progressing to active disease.

Diagnostic tests for LTBI

The tuberculin skin test (TST) has been the standard method of diagnosing LTBI. It involves measuring induration caused by a delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis* (Mtb) 2 or 3 days after injecting the reagent into the skin. The TST can result in false positives when detecting antibodies to BCG and nontuberculous mycobacteria, and false negatives when the patient does not demonstrate a robust immune response. A newer testing method is the Interferon Gamma Release Assay (IGRA), which involves phlebotomy, followed by a series of laboratory procedures that measure IFN-gamma release by T cells that have been sensitized to Mtb. The sensitivity of IGRA is similar to the TST, but it has better specificity; it is much less likely to react to antigens from BCG or nontuberculous mycobacteria. As detailed below, this guideline suggests a significantly more prominent role for IGRA, compared with previous recommendations.

Recommendation 1. Perform an IGRA, rather than a TST, in individuals 5 years or older who meet the following criteria: 1) are likely to be infected with Mtb; 2) have a low or intermediate risk of disease progression; 3) in whom it has been decided that testing for LTBI is warranted. A TST is an acceptable alternative, particularly if an IGRA is not available, is too costly, or is too burdensome. If an individual either has a history of BCG vaccination or is unlikely to return to have their TST read, then it is strongly recommended to use the IGRA as the test of choice.

Recommendation 2. There are insufficient data to recommend a preference for either a TST or an IGRA as the first-line diagnostic test in individuals 5 years or older who are likely to be infected with Mtb, who have a high risk of progression to active disease, and in whom it has been determined that diagnostic testing for LTBI infection is warranted; either test would be acceptable. In very high-risk patients, consider dual testing, with a positive result from either test (TST or IGRA) being considered positive.

Recommendation 3. Guidelines do not recommend testing for persons at low risk for Mtb infection. However, the authors recognize that testing in such persons may nevertheless be mandated in certain situations (for example in some school or child care settings). In these cases, the authors recommend performing an IGRA instead of a TST, to minimize the chance of a false-positive result, although a TST is an acceptable alternative. Furthermore, if the initial test is positive, they suggest performing a confirmatory test (either an IGRA or TST) and considering the person infected only if both tests are positive.

Dr. Skolnik is professor of family and community medicine at Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, and associate director of the family medicine residency program at Abington (Pa.) Jefferson Health. Dr. Clark is associate director of the family medicine residency program at Abington (Pa.) Jefferson Health.

Recommendation 4. The authors suggest performing a TST rather than an IGRA in healthy children less than 5 years of age for whom it has been decided that diagnostic testing for LTBI is warranted. This recommendation reflects the limited body of evidence regarding IGRA testing in young children and the apparent decreased sensitivity (that is, more false negatives) in this population, compared with TST use.

In the area of serial testing for TB infection, often done in health care and institutional settings, the guideline points out areas of uncertainty with IGRA testing. Specifically, the IGRA test is subject to variability in readings and boosting with antigen exposure that can complicate interpretation of apparent conversion on repeat testing. One longitudinal study showed conversion rates with IGRA to be six to nine times higher than that seen for the TST, and those conversions were thought to represent false-positive tests. The guideline concludes that, "There is insufficient information available to guide the establishment of definitive criteria for the conversion." The committee thought that a positive test in a low-risk individual was likely to be a false-positive result and recommended repeat testing. Because of the possibility of boosting with antigen exposure in situations where dual testing is anticipated, it may be preferable to obtain a specimen for IGRA prior to, or concurrently with TST placement.

Bottom line

Current guidelines suggest a more prominent role for IGRA in testing for LTBI, particularly when the likelihood of exposure is low and in situations where a person may have received BCG vaccination, or would be unlikely to return for TST reading.

Reference

Lewisohn DM et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Inf Dis. 2017;64(2):111-5.

FDA approves epinephrine autoinjector for infants

BY CATHERINE COOPER NELLIST
Frontline Medical News

The Food and Drug Administration approved an epinephrine autoinjector constructed specifically to treat life-threatening allergic reactions in infants and small children weighing 16.5-33 pounds.

The Auvi-Q 0.1 mg autoinjector by kaléo was approved after a priority review by the FDA, with features such as "a voice prompt system that guides a user with step-by-step instructions through the delivery process," according to a written statement from the company. This autoinjector has a shorter needle length and lower dose of epinephrine than other FDA-approved 0.15-mg and 0.3-mg epinephrine autoinjectors.

In a previous study of 51 infants with a mean weight of 24 pounds who were treated with a 0.15-mg epinephrine autoinjector with a standard 12.7-mm needle length, 43% were at risk of having the needle strike the bone. Unintentional injection of epinephrine into the intraosseous space can cause systemic absorption of the epinephrine and possible cardiac complications (Ann Allergy Asthma Immunol. 2017 Jun;118[6]:719-25.e1).

This new autoinjector with a shorter needle length was designed to obviate this problem, according to kaléo's statement.

The Auvi-Q 0.1 mg autoinjector should be available to patients in the first half of 2018, the company said.

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KALEO

Sleep apnea treatment may reduce risk of epileptic seizures

BY TED BOSWORTH
Frontline Medical News

WASHINGTON – In patients with epilepsy, treatment of obstructive sleep apnea with continuous positive airway pressure may lead to substantial and sustained reductions in seizure activity, according to data presented at the annual meeting of the American Epilepsy Society.

The reduction in seizure activity with continuous positive airway pressure (cPAP) in patients with epilepsy contributes to other evidence that poor sleep quality is an important but preventable risk factor for seizures, according to Thapanee Somboon, MD, a research fellow at the Sleep Disorders Center at the Cleveland Clinic in Ohio.

"We think many clinicians overlook the relationship of sleep to risk of seizures," Dr. Somboon said. "All patients with epilepsy should be checked for sleep disorders, including insomnia and sleep apnea, because these are associated with seizures and are easily treated."

In this study, which was characterized as the largest yet to evaluate the effect of cPAP on seizure activity, all 197 patients had epilepsy but only 122 had obstructive sleep apnea (OSA). Of those with OSA, 73 were treated with cPAP and 49 were not. An additional 75 patients with epilepsy but no OSA were also treated with cPAP. Seizure activity in all groups was evaluated over a period of 1 year.

Treatment success, defined as no seizure activity or at least a 50% reduction from baseline in seizure activity, was achieved in 85% of those with OSA treated with cPAP, 55% of those with OSA that did not receive cPAP, and 65% of those who were treated with cPAP but did not have OSA.

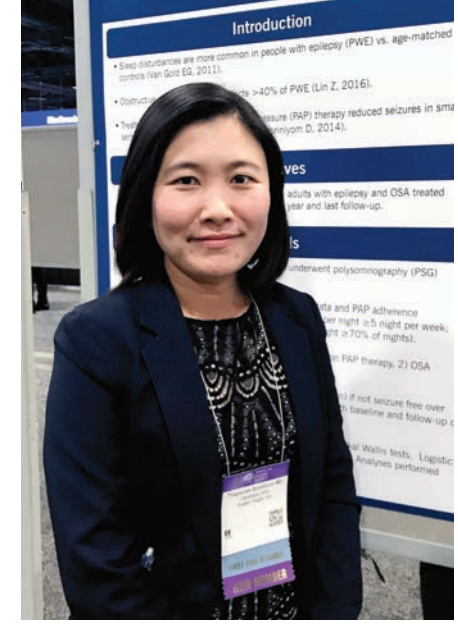
The difference was even greater among those with seizure activity in the 6 months prior to cPAP use. In these, a 50% or greater reduction in seizure activity was achieved in 63% of those with OSA treated with cPAP but in only 14% of those with OSA that did not receive cPAP. In the group without OSA, 44% achieved a 50% or greater reduction in seizure activity from baseline on cPAP.

"Epilepsy patients without OSA also appeared to benefit from cPAP, although prospective data are needed to further explore this observation," Dr. Somboon said.

All patients remained on antiepileptic drugs over the course of study, and the drug levels were not different between groups, according to Dr. Somboon. About half of all three groups were seizure free in the 6 months prior to cPAP. Those with OSA who received cPAP had a higher body mass index than did those who were not treated (34.6 vs. 31.1; *P* less than .001), but they were of similar age (47.6 vs. 47.9 years). Those without OSA who were treated with cPAP had a lower BMI (27.5; P less than .001) and were 10 years younger than were those with OSA (37.7 years; *P* less than .001). About two-thirds of all three groups had a history of focal seizures.

When expressed as odds ratios (OR), those treated for OSA had almost 10 times the likelihood of treatment success at 1 year (OR, 9.58; *P* less than .001), although being seizure free in the 6 months prior to cPAP had a 20-fold increased likelihood of treatment success (OR, 20.88; *P* less than .001).

Sleep disturbances and OSA are more common in patients with epilepsy than age-matched controls, according to Dr. Somboon, who cited published studies substantiating these statements. She noted that there are also previously published studies associating improved sleep hygiene, including improved sleep hygiene achieved with cPAP, with a reduced risk of seizure activity in epilepsy patients. However, at present there are no guideline recommendations for screening patients with epilepsy for OSA or other causes of impaired sleep, according to Dr. Somboon.



TED BOSWORTH/FRONTLINE MEDICAL NEWS
The link between sleep and seizure risk is overlooked suspects Dr. Somboon.

Although Dr. Somboon acknowledged that the data collected in this study cannot provide a definitive link between cPAP treatment, improved sleep, and reduced risk of seizure activity, this study does support these associations in the context of other evidence.

Dr. Somboon reported no financial relationships relevant to the study.

Phrenic-nerve stimulator maintains benefits for 18 months

BY MITCHEL L. ZOLER
Frontline Medical News

AT CHEST 2017 ▪ TORONTO – The implanted phrenic-nerve stimulation device that received Food and Drug Administration marketing approval in October 2017 for treating central sleep apnea has now shown safety and efficacy out to 18 months of continuous use in 102 patients.

After 18 months of treatment with the Remede System, patients' outcomes remained stable and patients continued to see the improvements they had experienced after 6 and 12 months of treatment. These improvements included significant average reductions from baseline in apnea-hypopnea index and central apnea index and significant increases in oxygenation and sleep quality, Andrew C. Kao, MD, said at the CHEST annual meeting.

"We were concerned that there would be a degradation of the benefit [over time]. We are very happy that the benefit was sustained," said Dr. Kao, a heart failure cardiologist at Saint Luke's Health System in Kansas City, Mo.

Dr. Kao's report focused on the 6-, 12-, and 18-month changes relative to baseline for five secondary outcomes: central sleep apnea index, apnea-hypopnea index, arousal index, oxygen desaturation index, and time spent in REM sleep. For all five of these outcomes, the 102 patients showed an average, statistically significant improvement compared with baseline after 6 months on treatment that persisted virtually unchanged at 12 and 18 months.


DR. KAO

For example, average central sleep apnea index fell from 27 events/hour at baseline to 5 per hour at 6, 12, and 18 months. Average apnea-hypopnea index fell from 46 events/hour at baseline to about 25 per hour at 6, 12, and 18 months. The average percentage of sleep spent in REM sleep improved from 12% at baseline to about 15% at 6, 12, and 18 months.

During 18 months of treatment following device implantation, four of the 102 patients had a serious adverse event. One patient required lead repositioning to relieve discomfort and three had an interaction with an implanted cardiac device. The effects resolved in all four patients without long-term impact. An additional 16 patients had discomfort that required an unscheduled medical visit, but these were not classified as serious episodes, and in 14 of these patients the discomfort resolved.

The Remede System phrenic-nerve stimulator received FDA marketing approval for moderate to severe central sleep apnea based on 6-month efficacy and 12-month safety data (Lancet. 2016 Sept 3;388[10048]:974-82). The Pivotal Trial of the Remede System enrolled 151 patients with an apnea-hypopnea index of at least 20 events/hour, about half of whom had heart failure. All patients received a device implant: In the initial intervention group of 73 patients, researchers turned on the device 1 month after implantation, and in the 78 patients randomized to the initial control arm, the device remained off for the first 7 months and then went active. The researchers followed up with 46 patients drawn from both the original treatment arm and 56 patients from the original control arm, at which point the patients had been receiving 18 months of treatment.

The Remede System pivotal trial was sponsored by Respicardia, which markets the phrenic-nerve stimulator. Dr. Kao's institution, Saint Luke's Health System, received grant support from Respicardia.

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New narcolepsy drug passes phase 3 test

BY JIM KLING
Frontline Medical News

SAN DIEGO – The selective dopamine and norepinephrine reuptake inhibitor solriamfetol is effective in reducing sleepiness in patients with narcolepsy, according to results of a phase 3 study.

At 150-mg and 300-mg doses, the drug had statistically significant effects on objective and subjective measures.

There are wake-promoting drugs available, such as amphetamine-related drugs that are often used off label, but addiction liability is a concern. The nonamphetamine modafinil has been approved by the Food and Drug Administration since 1998.

Jazz Pharmaceuticals is in the process of submitting solriamfetol for FDA evaluation. If approved, the drug will add to the options available for narcolepsy patients. "All of the available drugs have some limitations. Some have more abuse liability than others. Some have more robust wake-promoting properties than others. We haven't done any head-to-head comparisons, so I can't tell you how we will stack up," Philip Jochelson, MD, said in an interview. Dr. Jochelson is vice president of clinical development at Jazz Pharmaceuticals and presented the results of the study at a poster session at the annual meeting of the American Neurological Association.

An earlier study showed the drug had less abuse potential than the schedule IV stimulant phentermine. That's not surprising given the drug's mechanism of action, Dr. Jochelson said. Amphetamine-based drugs stimulate dopamine release, which can prompt a dopamine surge that people equate with a high, he said. Solriamfetol also affects dopamine, but it is a reuptake inhibitor, so it doesn't produce a surge.

If the drug gains approval, it remains to be seen how it will be classified on the Drug Enforcement Agency Controlled Substance scale. "Where it will fall in that spectrum is speculative at this point," said Dr. Jochelson.

In the current study, 236 adults (aged 18-75 years) with type 1 narcolepsy were randomized to once-daily placebo, 75 mg solriamfetol, 150 mg solriamfetol, or 300 mg solriamfetol; 27.1% of patients in the 300-mg group discontinued, compared with 7.3% in the 150-mg group, 16.9% in the 75-mg group, and 10.3% in the placebo group. The mean change from baseline on the Maintenance of Wakefulness Test was statistically significant in the 300-mg group (12.3 minutes vs. 2.1 minutes for placebo, *P* less than .0001) and the 150-mg group (9.8 minutes vs. 2.1 minutes, *P* less than .0001) but not the 75-mg group (4.7 minutes vs. 2.1 minutes).

The drug also outperformed placebo at week 12 on the Epworth Sleepiness Scale. The mean change in the 300-mg group was –6.4 vs. –1.6 for placebo (*P* less than .001), –5.4 in the 150-mg group (*P* less

"All of the available drugs have some limitations. Some have more abuse liability than others. Some have more robust wake-promoting properties than others. We haven't done any head-to-head comparisons, so I can't tell you how we will stack up."

than .0001), and –3.8 in the 75-mg group (*P* less than .05).

By both Maintenance of Wakefulness Test and Epworth Sleepiness Scale measures, the 150-mg and 300-mg solriamfetol groups had statistically significant differences as early as week 1.

The drug had some adverse effects, which were expected based on its pharmacologic profile. These included increases in headache (5.1% with placebo, 10.2% with 75 mg, 23.7% with 150 mg, 30.5% with 300 mg), nausea (1.7% for placebo, 5.1% for 75 mg, 10.2% for 150 mg, 16.9% for 300 mg), anxiety (1.7% with placebo, 1.7% with 75 mg, 5.1% with 150 mg, 8.5% with 300 mg), and insomnia (0% for placebo, 3.4% for 75 mg, 0% for 150 mg, 5.1% for 300 mg). Other adverse events occurring in at least 5% of patients were decreased appetite, nasopharyngitis, and dry mouth.

The study was funded by Jazz Pharmaceuticals. Dr. Jochelson is an employee of Jazz.

Role of Obstructive Sleep Apnea in HTN

BY SUPRIYA SINGH, MD; AND KANTA VELAMURI, MD

Heart disease and stroke are leading causes of death and disability. High blood pressure (BP) is a major risk factor for both.

The 2017 guidelines regarding "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure" (JNC 7) were recently published, which is an update incorporating new information from studies regarding BP-related risk of cardiovascular disease (CVD) and strategies to improve HTN (HTN) treatment and control.

Screening for secondary causes of HTN is necessary for new-onset or uncontrolled HTN in adults, including drug-resistant HTN. Screening includes testing for obstructive sleep apnea, which is highly prevalent in this population.

Obstructive sleep apnea is a common chronic condition characterized by recurrent collapse of upper airways during sleep, inducing intermittent episodes of apnea/hypopnea, hypoxemia, and sleep disruption (Pedrosa RP, et al. *Chest*. 2013;144[5]:1487).

It is estimated to affect 17% of US adults but is overwhelmingly underrecognized and untreated (*JAMA*. 2012;307[20]:2169). The prevalence is higher in men than women. The major risk factors for OSA are obesity, male sex, and advancing age. Since these conditions oftentimes predispose to and are concomitant with HTN, it can be challenging to determine the independent effects of OSA on the development of HTN.

The relationship between obstructive sleep apnea (OSA) and HTN has been a point of interest for decades, with untreated OSA being associated with an increased risk for developing new-onset HTN *(JAMA*. 2012;307[20]:2169).

There have been several landmark trials that have sought to determine the extent of a causal relationship between OSAS and HTN. Sleep Heart Health Study (*Sleep*. 2006;29;1009) was one such study, which was limited by the inability to prove that OSA preceded the onset of HTN.

Wisconsin Sleep Cohort (*N Engl J Med*. 2000;342:1378) was another landmark prospective longitudinal study that implicates OSA as a possible causal factor in HTN. The notable limitation of the study was the presence of HTN after initial assessment was found to be dependent upon the severity of OSA at baseline.

While these two cohort studies found an association between OSA and HTN, the Vitoria Sleep Cohort out of Spain (*Am J Respir Crit Care Med*. 2011;184[11]:1299), the third and most recent longitudinal cohort study, looked at younger and thinner patients than the SHHS and the Wisconsin Sleep Cohort, failed to show a significant association between OSA and incident HTN. Methodologic differences may help to explain the disparity in results.

NREM sleep has normal circadian


Dr. Singh is Director, Sleep Disorder and Research Center, Michael E. DeBakey VA Medical Center; and Dr. Singh is Assistant Professor and Dr. Velamuri is Associate Professor, Pulmonary, Critical Care and Sleep Medicine, Baylor College of Medicine. Houston, Texas.

variation of BP, causing "dipping" of both systolic and diastolic BP at night due to decreased sympathetic and increased parasympathetic activity. REM sleep has predominant sympathetic activity and transient nocturnal BP surges.

OSA results in hypoxemia, which causes nocturnal catecholamine surges, resulting in nocturnal increase in heart rate and BP that is most prominent during post-apneic hyperventilation.

Reduced nocturnal BP (nondipping) or even higher nocturnal BP than daytime BP is an undoubted risk factor for hypertensive patients due to the end-organ damage and subsequent cardiovascular events. With sleep apnea, sleep quality is decreased due to frequent arousal from sleep (*Hypertension.* 2006;47[5]:833).

Sleep duration of less than or equal to 5 hours per night was shown to significantly increase risk for HTN in patients less than or equal to 60 years of age, even after controlling for obesity and diabetes.

Sleep Heart Health Study suggests that sleep duration above or below a median of 7 to 8 hours per night is associated with a higher prevalence of HTN (*Sleep.* 2006;29:1009). Thus, improving duration and quality of sleep in sleep apnea patients may help decrease the risk of developing HTN.

Key question: Will treatment of OSA appreciably alter BP?

Continuous positive airway pressure (CPAP) is an efficacious treatment of choice for OSA. Interventional trials, though limited by issues related to compliance, have shown CPAP to acutely reduce sympathetic drive and BP during sleep. However, this improvement in BP control is not entirely consistent in all patients with the data being less clear-cut regarding nighttime CPAP therapy and impact on daytime BP.

A randomized controlled trial from Barbe et al suggests that normotensive subjects with severe OSA but without demonstrable daytime sleepiness are immune to the BP-reducing effects of CPAP (*Ann Intern Med.* 2001;134:1015); those who were objectively sleepy had a more robust response to the BP lowering effects of CPAP with better cardiovascular outcomes among patients who were adherent to CPAP therapy (≥4 hours per night).

Sleep Apnea Cardiovascular Endpoints (SAVE) study looked at CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea (*N Engl J Med.* 2016;375:919). CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood, but the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care compared with usual care alone. This study was not powered to provide definitive answers regarding the effects of CPAP on secondary cardiovascular end points, and the use of PAP was less than 4 hours.

A recent systematic review and meta-analysis looked at "Association of Positive Airway Pressure with Cardiovascular Events and Death in Adults with Sleep Apnea" (*JAMA.* 2017;318(2):156). No significant associations between PAP treatment and a range of cardiovascular events were noted in this meta-analysis.

It is possible that the limited adherence to therapy in many trials was insufficient to drive protection, along with short follow-up duration of most trials that may have given insufficient time for PAP to have affected vascular outcomes.

In a cross-over study of valsartan and CPAP, combining drug treatment with CPAP appeared to have a more synergistic effect in reducing BP than either agent alone (*Am J Respir Crit Care Med.* 2010;182:954).

The beneficial effect of CPAP remains an open question. Considering the multifactorial pathophysiology of OSA-associated HTN, proven therapies, such as BP lowering, lipid lowering, and antiplatelet therapy, along with PAP therapy, should be utilized. This combination strategy is likely to be more effective in improving both nocturnal and daytime BP control in OSA.

Yoga benefits lung cancer patients and caregivers

BY ANDREW D. BOWSER
Frontline Medical News

Yoga provides physical and mental benefits for both lung cancer patients and their caregivers, according to results of a randomized study presented at the Palliative and Supportive Care in Oncology Symposium.

"Overall, we are encouraged by the findings," said lead study author Kathrin Milbury, PhD, of University of Texas MD Anderson Cancer Center, Houston.

"We demonstrated that patients undergoing treatment for lung cancer are not too sick to participate in a behavioral supportive care intervention," Dr. Milbury said in a press conference. "Both patients and caregivers reported to have enjoyed the experience, and it gave them a time away from cancer, and [they] learned something new together."

This study provides preliminary evidence that a yoga program can provide a "buffer" and improve physical function for patients, as well as self-reported improved quality of life for both patients and their caregivers, she added.

All patients in the study had non–small cell lung cancer and were undergoing thoracic radiation therapy, which can cause respiratory toxicities that negatively affect quality of life and physical activity, according to Dr. Milbury and her coinvestigators.

A total of 32 patient-caregiver dyads were randomized to participate in 15 yoga sessions or to be in a "wait-list" control group, and 26 dyads completed all assessments.

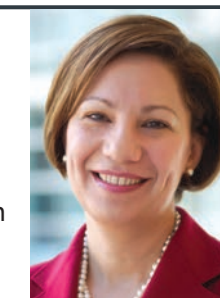
Patients who practiced yoga had significantly better scores on a 6-minute walking test (478 vs. 402 for wait-list enrollees; *P* less than .05), plus better stamina and mental health. Caregivers had improved fatigue and better stamina at work.

Almost all patients (96%) rated the program as "very useful," investigators reported at the symposium cosponsored by AAHPM, ASCO, ASTRO, and MASCC.

This study provides additional evidence that yoga and other nonpharmacologic supportive therapies "can be integrated into not only the care of cancer patients, but also the family caregivers who support them," according to Andrew S. Epstein, MD, of Memorial Sloan Kettering Cancer Center, New York.

Next, the researchers plan to conduct a larger, randomized controlled trial with a more stringent comparison group, according to Dr. Milbury.

VIEW ON THE NEWS



M. Patricia Rivera, MD, FCCP, comments: This is an interesting study further supporting the benefits of yoga and meditation when dealing with a chronic illness such as lung cancer. The benefits included reducing stress and improving quality of life, not only for the patient but also the caregiver.

Defining quality in lung cancer surgery

BY RICHARD MARK KIRKNER
Frontline Medical News

Implementing quality initiatives and creating reporting mechanisms for lung cancer patients can lead to better outcomes, including overall survival. While barriers exist – namely the conflicting perspectives of providers, payers, hospitals, and patients – thoracic oncologic surgeons should seize the opportunity to establish robust quality and value metrics for lung cancer programs, said Whitney S. Brandt, MD, and her coauthors in an expert opinion in the Journal of Thoracic and Cardiovascular Surgery (2017;154:1397-403).

Dr. Brandt, a surgeon at Memorial Sloan Kettering Cancer Center in New York, and her coauthors examined the key elements of quality and value initiatives, categorizing them into preoperative, intraoperative, and postoperative components and primarily focusing on early stage lung cancer.

The preoperative evaluation should at least include CT imaging of the tumor and, for smokers, smoking cessation, said Dr. Brandt and her coauthors. All candidates for pulmonary lung resection should have spirometry and diffusion capacity tests; furthermore, both predicted postoperative forced expiratory volume in 1 second and diffusing capacity of the lungs for CO should be calculated. "Patients with a predicted postoperative value less than 40% for either measurement should be considered high risk for lobectomy and should be offered either sublobar resection or nonsurgical therapy," they recommended.

Dr. Brandt and her colleagues also clarified preoperative management of patients with cardiac disease. Only patients with significant cardiac disease risk factors need to undergo cardiac testing before lung surgery, and patients with stable cardiac disease do not require revascularization beforehand.

For preoperative staging, the most comprehensive clinical guidelines come from the National Comprehensive Cancer Network, they stated. The guidelines recommend that all patients with a small cell lung cancer or stage II to IV non–small cell lung cancer (NSCLC) receive a brain MRI or – if that's not available – a head CT with contrast to assess for brain metastasis.

Intraoperative quality measures take into account the surgical approach, including cost, resection and margins, and lymph node evaluation. With regard to surgical approach, trials have shown traditional video-assisted thoracoscopic surgery (VATS) lobectomy results in shorter hospital stays and thereby lower costs, as well as fewer complications and deaths, than thoracotomy, said Dr. Brandt and her coauthors. But that cost advantage has not yet carried over to robotic-assisted VATS. That said, "robotic-assisted VATS remains a relatively new technology, and with time and increased robotic platform competition, costs will likely decrease."

Dr. Brandt and her coauthors also noted that clinical trials support resection margins of 2 cm in patients having surgery for NSCLC and that adequate lymph node evaluation is a critical component of a lung cancer quality initiative. "Regardless of whether lymph nodes are sampled or dissected, we believe that systematic acquisition of mediastinal nodal tissue based on nodal station(s) is a useful quality metric, and, therefore, we recommend each program adopt a preferred approach and track adherence," they said.

As for postoperative quality metrics, the most obvious are morbidity and mortality. "A quality program should track 30-day or in-hospital mortality, as well as 90-day mortality, following lung cancer resection." Such metrics can serve as "starting points" for quality improvement initiatives. Length of stay has also emerged as an important metric because it is a surrogate of other metrics, such as patient comorbidities, age, and socioeconomic status. "Length-of-stay metrics likely need to be risk-stratified on the basis of these and other variables to be meaningful to a practicing surgeon," Dr. Brandt and her coauthors said, adding that "studying the effectiveness of enhanced recovery after surgery programs in thoracic surgical oncology poses an opportunity for a well-designed trial."

Dr. Brandt and her coauthors reported no financial disclosures. The National Institutes of Health/National Cancer Center provided grant support.

VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Despite advances in diagnostic and therapeutic interventions, overall lung cancer survival remains low, and gains in survival over time have been modest. This is likely explained by advanced disease at the time of diagnosis although an alternative explanation is suboptimal care delivery. Although quality metrics and gaps may be difficult to measure due to challenges in defining quality, a better understanding of gaps in quality of care and disparities in the delivery of care is necessary in order to pursue quality improvement. As the authors point out in this study, in lung cancer surgery, adherence to known quality metrics such as guideline-based preoperative evaluation and systematic acquisition of mediastinal nodes results in improved patient outcomes.

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Indication

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

No dose adjustment required for renal impaired.

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

REVATIO is available in the following dosage forms:

- Tablets: 20 mg
- Injection: 10 mg/12.5 mL in a single use vial
- Oral Suspension: 10 mg/mL (when reconstituted)

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

Revatio® sildenafil

PP-REV-USA-0090-01

July 2016

Revatio® sildenafil 20 mg tablets

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

Safety data of REVATIO in adults were obtained from the 12-week, placebo-controlled clinical study (Study 1) and an open-label extension study in 277 REVATIO-treated patients with PAH, WHO Group I.

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

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

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

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

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

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

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

Ritonavir and other Potent CYP3A Inhibitors Concomitant use of REVATIO with ritonavir and other potent CYP3A inhibitors is not recommended.

Other drugs that reduce blood pressure *Alpha blockers.* In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO® (sildenafil).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

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

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

Pediatric Use In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

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

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

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

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

Patients with Renal Impairment No dose adjustment is required (including severe impairment CLcr <30 mL/min).

PATIENT COUNSELING INFORMATION

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

Rx only Rev. June 2015

Ultrathin bronchoscopy plus radial EBUS unreliable

BY MITCHEL L. ZOLER
Frontline Medical News

MITCHEL L. ZOLER/FRONTLINE MEDICAL NEWS

Dr. Nichole T. Tanner speaks at the CHEST annual meeting.

AT CHEST 2017 ▪ TORONTO – Ultrathin bronchoscopy plus radial endobronchial ultrasound is not a great method for determining whether a suspicious lesion is cancerous or benign, suggests new research.

In this study of patients with CT-detected solid lung lesions, the researchers were able to make a diagnosis for only 49% of those whose nodules were evaluated using ultrathin bronchoscopy plus radial endobronchial ultrasound (EBUS).

"You have a 50/50 chance" of making a diagnosis using an ultrathin bronchoscope plus radial EBUS, said Nichole T. Tanner, MD, FCCP, at the CHEST annual meeting. "I think you need to be thoughtful about how you use this technology," said Dr. Tanner, a pulmonologist and critical care medicine physician at the Medical University of South Carolina in Charleston.

"When you do CT-guided biopsies of lung lesions, the [diagnostic] yield is about 94%," she noted.

The study compared the diagnostic yield of ultrathin bronchoscopy plus radial EBUS with standard bronchoscopy and fluoroscopy in patients with CT-detected solid lung lesions 1.5-5.0 cm in size. It ran at five U.S. centers and randomized 221 patients: 85 evaluable patients were tested using the standard methods and 112 evaluable patients were tested using ultrathin bronchoscopy plus radial EBUS. Patients averaged 65-68 years of age and were divided evenly between women and men. Their lesions averaged slightly more than 3 cm. The ultrathin device had a 4-mm-wide diameter and had a 2-mm working channel.

The diagnostic yield was 38% among patients who underwent standard bronchoscopy and fluoroscopy and 49% among those biopsied using ultrathin bronchoscopy and radial EBUS, Dr. Tanner reported. The between-group difference in yield fell short of being statistically significant.

Forty-six of the 53 patients who were not diagnosable using standard bronchoscopy and fluoroscopy crossed over to the investigational method, which produced a diagnosis for an additional seven patients (15% of the biopsied crossover patients).

Dr. Tanner disclosed financial relationships with several companies, including having served as a consultant to and received research funding from Olympus, which funded this study.

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VIEW ON THE NEWS

M. Patricia Rivera, MD, FCCP, comments: Although bronchoscopic tools are safe and accurate to evaluate both central and peripheral lung lesions, the diagnostic yield of the different available techniques is variable. In this study, a diagnostic yield of only 49% was achieved when ultrathin bronchoscopy with radial EBUS was performed for diagnosis of solid nodules. This yield is not much better than that obtained from conventional bronchoscopy with fluoroscopic guidance and much lower than the diagnostic yield from transthoracic needle biopsy. While there is no doubt that the advances in minimally invasive technologies for diagnosing lung nodules and diagnosing and staging lung cancer have revolutionized clinical practice, pulmonologists and thoracic surgeons need to recognize not only the utility but also the limitations of the available diagnostic procedures (as well as the cost). These technologies are complimentary and multidisciplinary discussions should facilitate selection of the best procedure for each individual case.

This Month in *CHEST*®

Editor's Picks

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

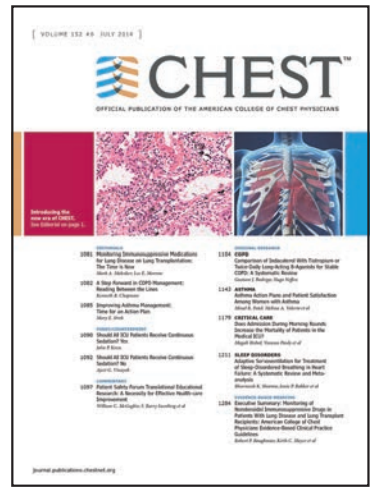
EDITORIAL
Introducing the CHEST Teaching, Education, and Career Hub
Dr. G. T. Bosslet and Dr. M. Miles

TRAINING, EDUCATION, AND CAREER HUB - TEACH
Strategies for Success in Fellowship
Dr. R. W. Ashton, et al.

COMMENTARY
Higher Priced Older Pharmaceuticals: How Should We Respond?
Dr. R. S. Irwin, et al.

GIANTS IN CHEST MEDICINE
Jeffrey M. Drazen, MD, FCCP
Dr. A. S. Slutsky

EVIDENCE-BASED MEDICINE
Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report
Dr. R. S. Irwin, et al.



ORIGINAL RESEARCH
Three-Hour Bundle Compliance and Outcomes in Patients With Undiagnosed Severe Sepsis
Dr. A. S. Deis, et al.

A Phase II Clinical Trial of Low-Dose Inhaled Carbon Monoxide in Idiopathic Pulmonary Fibrosis
Dr. I. O. Rosas, et al.

New CHEST Physician Leadership for 2018

David A. Schulman, MD, FCCP, is the new Editor in Chief of *CHEST Physician*. He is a Professor in the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine at Emory University in Atlanta, where he also directs the pulmonary and critical care fellowship program. He has served on the CHEST Sleep Net-Work and the Education Committee and currently serves on the Training and Transitions Committee and the Board of Regents. Dr. Schulman's primary area of academic interest is on faculty development in the domains of teaching and assessment. He will serve as the Chair of the CHEST 2018 Scientific Program Committee, where he will focus on crafting novel, interactive programming that will improve attendee engagement and retention.


DR. SCHULMAN

What are the top three things Dr. Schulman hopes to accomplish as Editor in Chief of *CHEST Physician*?

1 Improve interactivity between CHEST Physician and its readership, to improve our ability to craft the publication that best meets the needs of its readers.
2 Create more opportunities for CHEST Physician to serve as the voice of CHEST members, by increasing space for members and leaders to write for the publication.
3 Build on the incredibly successful work of my predecessor, Dr. Vera DePalo.

Christopher Lettieri, MD, FCCP, is the new Section Editor for Sleep Strategies. He is a Professor of Medicine, Division of Pulmonary and Critical Care Medicine, at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. Dr. Lettieri has previously served as the Chief and Medical

DR. LETTIERI

Director of the Sleep Disorders Center at the Walter Reed National Military Medical Center, and as the Program Director for the National Capital Consortium's Sleep Medicine Fellowship training program. He is currently assigned as the Pulmonary and Critical Care Consultant to the Army Surgeon General, and as the Director of Global Health and Senior Clinical Advisor to the Joint Chiefs of Staff. Dr. Lettieri's research interests include enhancing PAP adherence and improving outcomes in sleep disorders related to PTSD and TBI.

Angel Coz, MD, FCCP, is the new Section Editor for Critical Care Commentary. He is an Associate Professor of Medicine at the University of Kentucky and the Lexington Veterans Affairs Medical Center. He is the Chair of CHEST's Critical Care NetWork and has served in the Clinical Pulmonary Medicine NetWork Steering Committee and the Nominating Committee. He has led ICU quality improvement initiatives, including early detection and aggressive management of sepsis. Dr. Coz interests include medical education, sepsis, and ICU quality improvement. He has given multiple talks on sepsis and critical care topics nationally and internationally. He was recently recognized as a Distinguished CHEST Educator. Dr. Coz was very active also in developing the simulation-based difficult airway course for CHEST.

DR. COZ

CHEST extends very special thanks to the following *CHEST Physician* editors for their 3 years of dedicated service in the following roles:

Vera de Palo, MD, FCCP – *Editor in Chief*
Lee Morrow, MD, FCCP – *Section Editor for Critical Care Commentary*
Jeremy Weingarten, MD, FCCP – *Section Editor for Sleep Strategies*

Live Streaming at CHEST 2017

BY KRISTI BRUNO
CHEST *Director of Communications, Media, and Marketing*

In April 2016, Facebook launched Facebook Live, a tool for live streaming to a Facebook page to share live video with their followers on Facebook. At CHEST 2016, the CHEST New Media team began to experiment with live video with some early success. The CHEST 2017 team made the decision, based on the organization's goal to help educate clinicians to improve patient care, to live stream complete sessions from CHEST 2017. With the help of the CHEST 2017 Education Committee and the Social Media Work Group, more than 25 sessions were selected and live streamed.

CHEST's efforts on Facebook Live resulted in the following:

- Total people reached: 133,737
- Total video views: 34,449
- Total minutes watched: 30,786 (or 513 hours, or 21 days)
- Total interactions: 1,050 (eg, likes, loves, hahas, etc)
- Total shares: 302

The content concept was well received, and comments ranged from followers chiming in with their location, appreciation for live streaming, and even comments from patients.

- "Thank you for sharing this live presentation."
- "Here from Mexico !!"
- "Here from Natal/RN, Brazil"
- "Here from Milan, Italy."
- "Appreciate this live streaming on important sessions, big service for those who couldn't attend!!"
- "My brother survived after six days on ECMO. I am so glad to have him."
- "It's a great chance for physicians working in pulmonology and general practice to get the pearls of guidelines from American College to improve clinical practice. Now distance doesn't matter"

Plans are underway for live streaming from CHEST 2018 in San Antonio. To view the CHEST 2017 live stream videos, visit CHEST's Facebook page, facebook.com/accpchest.

Winners-All at CHEST 2017

With the great success of CHEST 2017, everyone who shared that event is a winner. But, we would especially like to call out some of the special winners who were recognized during our meeting in Toronto.

CHEST 2017 Awards

- **College Medalist Award**
  Sidney Braman, MD, Master FCCP
- **Distinguished Service Award**
  Nancy Collop, MD, FCCP
- **Master FCCP**
  Suhail Raoof, MD, Master FCCP
- **Master FCCP**
  Sidney Braman, MD, Master FCCP
- **Early Career Clinician Educator**
  Septimiu Murgu, MD, FCCP
- **Master Clinician Educator**
  Stephanie Levine, MD, FCCP
- **Presidential Citation**
  Sanjeev Mehta, MD, FCCP
- **Presidential Citation**
  Lisa Moores, MD, FCCP
- **Alfred Soffer Award for Editorial Excellence**
  Christopher Carroll, MD, FCCP
  Deep Ramachandran, MBBS

Honor Lectures

- **Thomas L. Petty, MD, Master FCCP Memorial Lecture**
  Personalized Treatment in COPD: A New Era of Treatment Options
  Gerard J. Criner, MD, FCCP
- **Presidential Honor Lecture**
  Passion, Perseverance, and Quantum Leaps: Major Advances in Lung Cancer Care
  M. Patricia Rivera, MD, FCCP
- **Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation**
  When Air becomes BREATH…and a LIFE worth living
  Audrey King, MA
- **Distinguished Scientist Honor Lecture in Cardiopulmonary Physiology**
  Sleep, Death and the Heart
  Virend K. Somers, MD, PhD, FCCP
- **Pasquale Ciaglia Memorial Lecture in Interventional Medicine**
  Augmented Reality: Getting Real in Procedural Education
  Carla R. Lamb, MD, FCCP
- **Roger C. Bone Memorial Lecture in Critical Care**
  If You've Seen One ICU You've Seen All ICUs: Evidence-based Recommendations for the Organization of Critical Care
  Gordon D. Rubenfeld, MD, MS
- **Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture**
  "Pills" and the Air Passages
  Atul C. Mehta, MBBS, FCCP
- **Murray Kornfeld Memorial Founders Lecture**
  Trying to Change Clinical Practice: The Barcelona Respiratory Research Group
  Antonio Torres Marti, MD, PhD, FCCP

CHEST Foundation Grant Awards

- **CHEST Foundation Research Grant in Nontuberculous Mycobacteria**
  Keira Cohen, MD
- **CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency**
  Diana Crossley, MBChB
- **CHEST Foundation Research Grant in Asthma**
  Drew Harris, MD
- **CHEST Foundation Research Grant in Pulmonary Fibrosis**
  Kerri Johannson, MD, MPH
- **CHEST Foundation Research Grant in Women's Lung Health**
  Stephen Lapinsky, MBBCh, MS
- **CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease**
  Emmet O'Brien, MBBCh
- **CHEST Foundation Research Grant in Venous Thromboembolism**
  Christopher Pannucci, MD
- **CHEST Foundation Research Grant in Cystic Fibrosis**
  Kathleen Ramos, MD, MS
- **CHEST Foundation Research Grant in Pulmonary Arterial Hypertension**
  Sandeep Sahay, MD, FCCP
- **CHEST Foundation Research Grant in Lung Cancer**
  Kei Suzuki, MD
- **GlaxoSmithKline Distinguished Scholar in Respiratory Health**
  Richard Wunderlink, MD, FCCP
- **CHEST Co-Branded Community Service Initiatives**
  Sandra Adams, MD, MS, FCCP
  Mary Hart, RRT, MS, FCCP
- **GAIN NSCLC Summits Community Service Grant**
  J. Scott Ferguson, MD, FCCP
- **CHEST Foundation Community Service Grants** *Honoring D. Robert McCaffree, MD, Master FCCP*
  Negin Hajizadeh, MD, MPH
  Adam Silverman, MD

Case Report Poster Winners

Javier Ramos Rossy, MD
Bikash Bhattarai, MD
Nikita Leiter, MD
Lindsay Boole, MD, MPH
Muhammad Hammami, MD
Jonathan Dewald, MD
Ahmed Mahgoub, MD
Ali Saeed, MD
Aditya Kotecha, MD
David Attalla, MD

CHEST Challenge Winners

San Antonio Military Medical Center
David Anderson, DO
Paul Hiles, MD, BSc
Tyson Sjulin, DO

Alfred Soffer Research Award Winners

- Marcos Restrepo, MD, MSc, FCCP: *Anti-MRSA Coverage Overutilization as Empiric Therapy for Hospitalized Patients With Community-acquired Pneumonia and Health-care Associated Pneumonia*
- Michael Perkins, MD: *Rothman Index Predicts ICU Mortality at 24 hours*

Young Investigator Award Winners

- Adam Przebinda, MD: *Analysis of a Hospital-based Multimodal Quality Improvement Intervention to Improve Recognition and Treatment of Sepsis*
- Roozehra Khan, DO, FCCP: *Growth in Social Media & Live-Tweeting at Major Critical Care Conferences: Twitter Analysis of Past 4 Years*

Top 5 Slide Presentation Winners

- Jonathan Corren, MD: *Dupilumab Improves Asthma Control and Asthma-Related Quality of Life in Uncontrolled Persistent Asthma Patients Across All Baseline Exacerbation Rates*
- Aaron B. Holley, MD, FCCP: *Heparin prophylaxis does not prevent VTE in the presence of acute kidney injury*
- Anil Vachani, MD, FCCP: *A Blood-based Multi-gene Expression Classifier to Distinguish Benign from Malignant Pulmonary Nodules*
- Abhishek Mishra, MD: *Comparison of Catheter directed thrombolysis vs systemic thrombolysis in pulmonary embolism: A propensity score match analysis*
- David E. Ost, MD, MPH, FCCP: *Comparison of Practice Patterns and Outcomes for Recurrent Malignant Pleural Effusions*

Case Report Slide Winners

- Christian Castaneda, MD: *Levofloxacin-Induced Acute Eosinophilic Pneumonitis: A Case Report And Review*
- Lucian Marts, MD: *The Proof Is In The Platelets*
- Fuad Aleskerov, MD: *Disseminated Resistant Nocardiosis In Previously Healthy Male*
- Taylor Myers, MD: *Spontaneous Regression Of Non-Small Cell Lung Cancer*
- Amin Pasha, MD: *Is Fat Always Bad? A Case Study Demonstrating The Lifesaving Effect Of Lipid Emulsion Therapy In Beta Blocker And Calcium Channel Blocker Overdose*
- Anish Geevarghese, MD: *The Use Of Venovenous-ECMO For Refractory Hypoxemia Following Liver Transplantation In A Patient With Hepatopulmonary Syndrome*
- Juilio Huapaya, MD: *Hemophagocytic Lymphohistiocytosis Induced By Histoplasmosis In A Kidney Transplant Patient: Are Steroids Really Necessary?*
- Stephen Doyle, DO, MBA: *Diffuse Pulmonary Nodules: A Rare Infection Causing A Common Problem*
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NetWork Challenge Winners

- First Round: *Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork, and Women's Health NetWork*
- Second Round: *Home-Based Mechanical Ventilation and Neuromuscular Disease and Practice Operations*
- Third Round: *Home-Based Mechanical Ventilation and Neuromuscular Disease and Practice Operations*

Another Small Win to Raise the Tobacco Purchasing Age to 21

BY KIM FRENCH, MHSA, CAPPM
CHEST Foundation Trustee

The Elk Grove Village, Illinois, Board of Trustees passed the "Tobacco 21" ordinance that will raise the tobacco purchasing age to 21, which includes nicotine vaping. The policy, which will go into effect January 1, 2018, will protect young people from beginning a lifetime of addiction and, ultimately, save their lives.

Kevin L Kovitz MD, MBA, FCCP, attended the Village Board meeting to advocate for "Tobacco 21." He is a Sustaining Member of the CHEST Foundation, continually exemplifying what it is to be a lung health champion.

Dr. Kovitz noted, "This policy will protect our kids from the scourge of Big Tobacco and save funding for health-care costs and, most importantly, will ultimately save lives. The ordinance will protect the most vulnerable parts of our population, our children. Raising the legal age puts tobacco products on par with alcohol and protects young adults from developing a dangerous lifelong habit."

Five US states have also passed Tobacco 21; they include California, Hawaii, Maine, New Jersey, and Oregon. There are many local ordinances around the country but more are needed.

Advocating for this ordinance demonstrates the effectiveness of grassroots advocacy in our local communities.

Smart Ways to Give More Now

Your gift today truly has an immediate impact that makes a difference now.

We also want you to benefit as much as possible from your generosity.

Gifts of Appreciated Securities, Mutual Funds, and Investments

If you have owned any of these longer than 1 year and they have appreciated in value, they provide a smart option for gifting. You will avoid the capital gains tax, and you also receive a charitable income tax deduction if you itemize your tax return.

The Charitable Individual Retirement Plan Option

If you are 70 1/2, you may distribute funds from your IRA directly to the CHEST Foundation.

You will not pay any income taxes, and it will also qualify for your required minimum withdrawal. You may distribute up to $100,000 per person per year ($200,000 if you are married and both own an IRA).

Retirement Plan Beneficiary Designation

You may also designate a charity as a beneficiary of your IRA, 401K, or 403B.

This will avoid any income tax, so 100% will be directed to the charity of your choice.

For more information on these and other ways to support the CHEST Foundation, confidentially and with no obligation, contact Angela Perillo, CHEST Director of Development & Foundation Operations, at aperillo@chestnet.org.

INDEX OF ADVERTISERS

News From American Association of Critical-Care Nurses (AACN)

AACN has published a new edition of "AACN Scope and Standards for Acute Care Nurse Practitioner Practice" to reflect the specialty's evolving role and an ever-changing critical care landscape.

First issued in 2006 and previously updated in 2012, the new edition describes and measures the expected level of practice and professional performance for acute care nurse practitioners (ACNPs). The 2017 edition, which came from collaboration from a work group of ACNP subject matter experts convened by AACN collaborated to update the content to reflect current practice incorporates advances in scientific knowledge, clinical practice, technology and other changes in the dynamic healthcare environment. It addresses the full scope of practice for ACNPs, including those whose education and training prepare them to care for children with acute and critical illnesses. It also aligns with the "Consensus Model for APRN Regulation" — also called the LACE Model — developed to create national congruence for licensure, accreditation, certification, and education of advanced practice nurses.

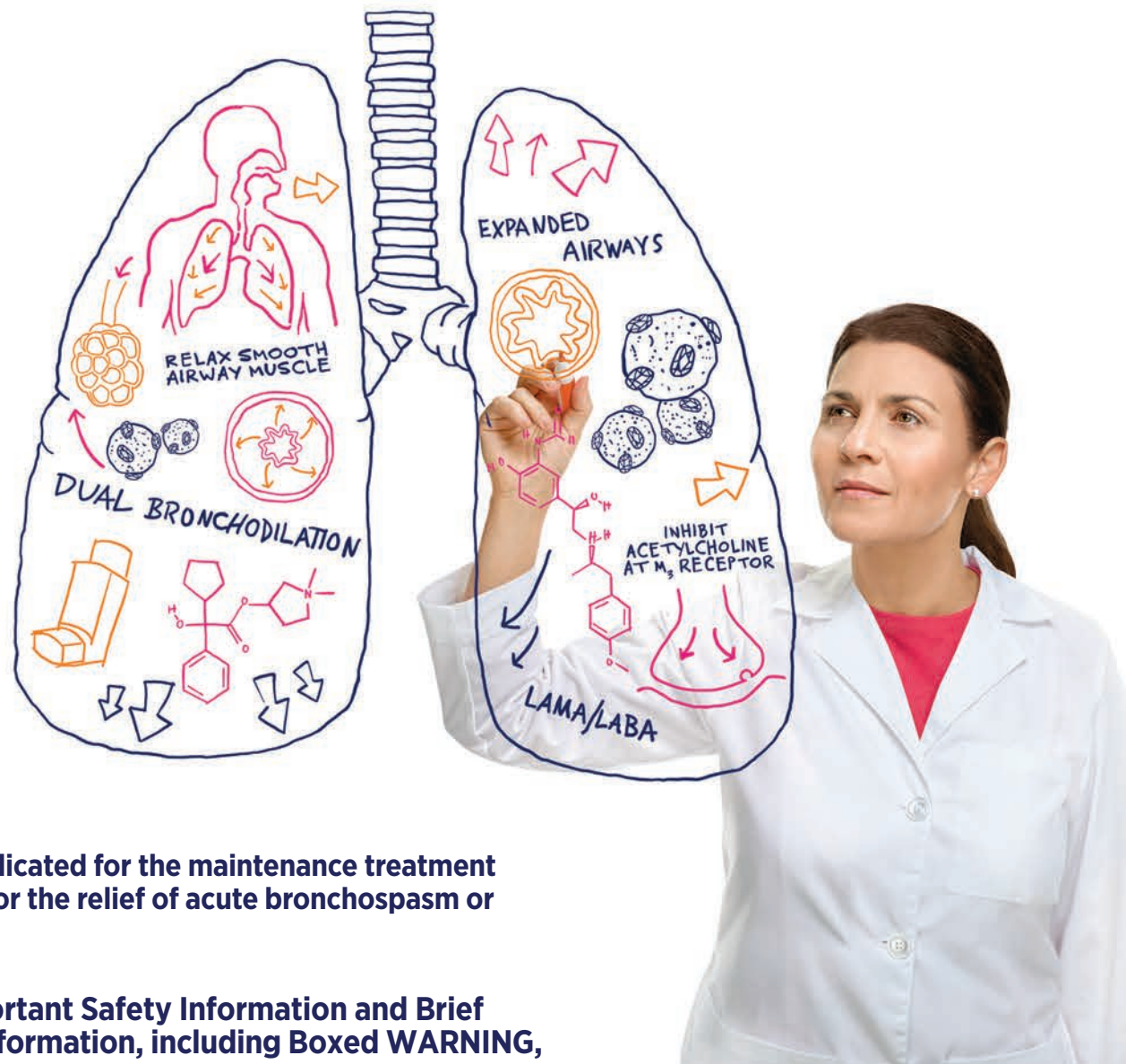
"The role of acute care nurse practitioners continues to expand as more hospitals and healthcare organizations discover the value of having ACNPs on staff," said Linda Bell, AACN clinical practice specialist and editor of the publication. "Patients who used to be hospitalized are now cared for throughout the healthcare system. As a result, the services or care provided by ACNPs and other advanced practice providers are not defined or limited by setting but rather by patient care needs."

These standards are a valuable resource for acute care pediatric nurse practitioners (CPNP-AC), adult ACNPs (ACNPC-AG or ACNP-BC) and those developing educational programs for advanced nursing practice, job descriptions and credentialing, among other uses.

New edition of ACNP Scope and Standard is available from American Association of Critical-Care Nurses (aacn.org).

BEVESPI AEROSPHERE®

(glycopyrrolate 9 mcg/
formoterol fumarate 4.8 mcg)
Inhalation Aerosol



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

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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

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

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS: The most common adverse reactions with BEVESPI (≥2% and more common than placebo) were: cough, 4.0% (2.7%), and urinary tract infection, 2.6% (2.3%).

DRUG INTERACTIONS

- Use caution if administering additional adrenergic drugs because the sympathetic effects of formoterol may be potentiated
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of formoterol
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant $beta_2$-agonists
- The action of adrenergic agonists on the cardiovascular system may be potentiated

BEVESPI AEROSPHERE FOR THE MAINTENANCE TREATMENT OF COPD

DUAL BRONCHODILATION, DOWN TO A SCIENCE

2017 GOLD Report

LAMA/LABAs RECOMMENDED

1ST-LINE FOR MOST PATIENTS*

MAXIMIZE BRONCHODILATION[1,2†]

Improved lung function including predose FEV_1 and peak FEV_1 at 24 weeks[1,2‡]

In a separate study vs placebo, improvement in peak inspiratory capacity at Day 29[3§‖]

INTELLIGENT FORMULATION[1¶]

Intelligent formulation for a pMDI using patented, phospholipid-based AEROSPHERE™ Delivery Technology[1]

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

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

*Initial treatment in Group B patients with severe breathlessness and in Group D patients.

†Defined as superior improvement in lung function with BEVESPI AEROSPHERE vs its individual components and placebo in two 24-week pivotal trials (n=3699).

‖In a separate Phase IIIb trial (n=35), there was a significant improvement in the primary endpoint, FEV_1 $AUC_{0\text{-}24}$, on Day 29 vs placebo. Peak inspiratory capacity after the evening dose on Day 29 was a secondary endpoint. Similar results seen in a second Phase IIIb trial (n=75).

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

by monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval. Therefore, BEVESPI should be used with extreme caution in patients being treated with these agents

- Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD
- Avoid co-administration of BEVESPI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects

INDICATION: BEVESPI AEROSPHERE is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting $beta_2$-adrenergic agonist (LABA), indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

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

‡**PINNACLE 1 & 2 Pivotal Trials:** Two 24-week efficacy and safety studies were conducted in patients with moderate to very severe COPD (n=3699). Inclusion criteria: A clinical diagnosis of COPD; between 40-80 years of age; history of smoking ≥10 pack-years; post-albuterol FEV_1 of <80% of predicted normal values, and FEV_1/FVC ratio <0.7. The primary endpoint was change from baseline in trough FEV_1 at Week 24 for BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID (150 mL), glycopyrrolate 18 mcg BID (59 mL), and formoterol fumarate 9.6 mcg BID (64 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Trial 1 also included an open-label active control.[1] Statistically significant results were also seen in Trial 2.[1,2] Secondary endpoints included change from baseline in peak FEV_1 at Week 24 for BEVESPI BID compared with placebo BID (291 mL), glycopyrrolate 18 mcg BID (133 mL), and formoterol fumarate 9.6 mcg BID (93 mL); results are from Trial 1; *P*<0.0001 for all treatment comparisons.[1,2] Statistically significant results were also seen in Trial 2.[1,2]

§**Separate Phase IIIb Trials (Study A & B):** Two Phase IIIb crossover studies were conducted to evaluate the 24-hour lung function profile of BEVESPI 18 mcg/9.6 mcg BID compared with placebo BID in patients with moderate to very severe COPD after 4 weeks of chronic dosing (Study A and Study B). Study B also included an open-label active control.[3] Inclusion criteria were consistent with the two 24-week pivotal trials.[1,3] Adverse events were numerically similar across treatment arms.[3] Primary endpoint, FEV_1 $AUC_{0\text{-}24}$: Study A – BEVESPI (n=35) vs placebo (n=31) = 249 mL (baseline FEV_1 1.382 L and 1.345 L, respectively); Study B – BEVESPI (n=65) vs placebo (n=65) = 265 mL (baseline FEV_1 1.328 L and 1.333 L, respectively); both *P*<0.0001.[4] Secondary endpoint, Peak IC (evening): Study A – BEVESPI (n=34) vs placebo (n=30) = 381 mL (baseline IC [evening], 1.980 L and 1.939 L, respectively); Study B – BEVESPI (n=62) vs placebo (n=63) = 312 mL (baseline IC [evening] 1.877 L and 1.913 L, respectively); both *P*<0.0001.[4]

References: 1. BEVESPI AEROSPHERE [Package Insert]. Wilmington, DE: AstraZeneca; 2017. **2.** Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340-357. **3.** Reisner C, Gottschlich G, Fakih F, et al. 24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD. *Respir Res*. 2017;18:157. **4.** Data on File, 3270300, AZPLP.

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

Learn more at DUALBRONCHODILATION.COM

AstraZeneca

BEVESPI AEROSPHERE™

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

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

WARNING: ASTHMA-RELATED DEATH

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

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

INDICATIONS AND USAGE

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

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

DOSAGE AND ADMINISTRATION

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

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

Asthma-Related Death

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

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

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

Deterioration of Disease and Acute Episodes

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

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

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

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

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

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

Paradoxical Bronchospasm

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

Immediate Hypersensitivity Reactions

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

Cardiovascular Effects

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

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

Coexisting Conditions

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

Hypokalemia and Hyperglycemia

Beta$_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. The decrease in serum potassium is usually transient, not requiring supplementation. Beta$_2$-agonist medicines may produce transient hyperglycemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ADVERSE REACTIONS

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

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

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

Clinical Trials Experience

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

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

24-Week Trials

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

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

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

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

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

Long-Term Safety Extension Trial

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

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

DRUG INTERACTIONS

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

Adrenergic Drugs

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

Xanthine Derivatives, Steroids, or Diuretics

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

Non-Potassium Sparing Diuretics

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

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

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

Beta-Blockers

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

Anticholinergics

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects:

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

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

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

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

Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 61,000 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 60 mg/kg/day in rabbits). No teratogenic effects were observed at approximately 3600 times the MRHDID (on a mg/m^2 basis at maternal oral doses up to 3.5 mg/kg/day).

Labor and Delivery

There are no well-controlled human trials that have investigated the effects of BEVESPI AEROSPHERE on preterm labor or labor at term. Because $beta_2$-agonists may potentially interfere with uterine contractility, BEVESPI AEROSPHERE should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

Glycopyrrolate

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

Formoterol Fumarate

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

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
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or By: AstraZeneca Dunkerque Production (AZDP), Dunkerque France

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CHEST President, Dr. John Studdard on the Search for a New Editor in Chief for *CHEST*®

CHEST®, the flagship peer-reviewed journal of the American College of Chest Physicians (CHEST), is seeking applicants for the next Editor in Chief (EIC). President of CHEST, Dr. John Studdard, has given some insight into the successes of the journal during current EIC, Dr. Richard Irwin's tenure, and what we can expect from the respected individual who will take his place in 2019.

"From my perspective as a community-based physician practicing pulmonary, critical care, and sleep medicine, I believe the responsibility of member-based organizations like CHEST is to ensure that we create meaningful science, create outstanding education, and work to ensure these are disseminated and implemented. One of the most important vehicles that we depend on is our *CHEST*® journal.

DR. STUDDARD

CHEST® is more than just a medical journal; it is the face and brand of the American College of Chest Physicians. Recognition and awareness of the journal as the face of the organization is an incredibly important aspect of what it means to the CHEST organization as a whole."

Dr. Studdard's insights as to some of the successes and the future of *CHEST*®:

Question: What is your view on the successes of the journal over Dr. Irwin's tenure?

Answer: A. The journal consistently ranks as the #1 relevant journal for respiratory clinicians and providers.

B. The journal's "impact factor" has increased significantly, which supports its efforts to attract the best clinical research and content.

C. New sections added provide applicable clinical information, address hot and controversial topics, and underscore the human side of medicine to support the best patient-focused care.

D. The continual improvement of our online platform, including development of multimedia content and other innovations that take advantage of the digital evolution of online content delivery.

E. Last, but not least, I believe our members who are clinicians consider *CHEST*® to be the one journal to review cover to cover and to be their "go to" journal for relevant clinical insights and information.

Question: What challenges does CHEST expect the next EIC to be facing?

Answer: We clearly practice in an environment where there are constant pulls for the time and attention of clinicians … a constant influx of information and education in multiple formats and delivery systems. The journal *CHEST*® must highlight the information we need most that will impact patient care. Our new EIC, and the team assembled, will need to solicit the best research, continue our digital evolution, and ensure they are delivering this infor-

Continued on following page

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PROFESSIONAL OPPORTUNITIES

NETWORKS

BP targets questioned, *Candida auris* infections

Cardiovascular Medicine and Surgery

The Holy Grail of Blood Pressure Management?

Blood pressure treatment recommendations have been confusing over the past few years. The Joint National Committee (JNC) 8 stirred up controversy in 2014 because they raised the recommended tolerating systolic blood pressures, in certain people aged 60 and above, up to 150 mm Hg [James, et al. JAMA. 2014;311(5):507-520]. The new AHA/ACC hypertension guidelines cosponsored by 11 societies generated controversy because they changed the definition of hypertension (normal <120/80 mm Hg, elevated 120-129/80-89, stage 1 130-139/80-89, or stage 2 >140/90) [Whelton et al. J Am Coll Cardiol. 2017 pii:S0735-1097(17)41519-1]. The SPRINT trial [Wright, et al. N Engl J Med. 2015;373:2103-2116] largely influenced these recommendations. SPRINT demonstrated a 25% relative risk reduction of heart attack, stroke, cardiovascular death, or decompensated heart failure with more aggressive blood pressure management (BP goal <120/90 vs <140/90).

This new classification would label 46% of Americans, or 103.3 million people, as hypertensive. However, there is uncertainty in how broadly applicable the SPRINT results are, particularly in those under the age of 45. The majority of large clinical trials, including SPRINT, have limited numbers of patients who were less than 50 years old and, therefore, it is unknown if younger patients benefit to the same degree. The absolute improvement is also questionable because as an editorial points out [Welch, "Don't Let New Blood Pressure Guidelines Raise Yours" NY Times. Nov. 15, 2017], the primary endpoint in SPRINT only occurred in less than or equal to 8% of patients.

These guidelines reinforce the need to measure ambulatory blood pressures, perform proper in-office blood pressure measurements, and emphasize lifestyle modifications. Whether aggressive blood pressure management is worth the potential risks and the degree to which ideal blood pressure measurement can be applied to real world practices, remains uncertain.

David J. Nagel, MD, PhD
Steering Committee Member

Chest Infections

Candida auris

Invasive fungal infections are frequently managed by ICU physicians and are a leading cause of mortality among critically ill patients. Invasive candidiasis is associated with an attributable mortality rate of up to 49%. Historically, the majority of these infections has been caused by Candida albicans, but this may be changing.

The first outbreak of *Candida auris* in the Americas (18 patients) occurred in the ICU of a hospital in Venezuela. Resistance to common azoles was documented, and half of the isolates showed decreased susceptibility to amphotericin B. As of August 2017, a total 153 clinical cases of *C auris* infection have been reported to CDC from 10 US states; most have occurred in New York and New Jersey.

What has been learned from these cases is that close contacts can be colonized, colonization can be persistent (approximately 9 months), the yeast can survive in the hospital environment, bleach or sporicide is needed for elimination, isolation precautions are recommended as for MDRO bacteria, and serial resistance to echinocandins has been observed.

Principal takeaways:

1. *Candida auris* isolates are often MDR, with some strains having elevated MICs to drugs in all the three major classes of antifungal medications.
2. The isolates are difficult to identify and require specialized methods, such as MALDI-TOF or molecular identification based on sequencing.
3. Misidentification may lead to inappropriate treatment.
4. *C auris* has the propensity to cause outbreaks in health-care settings, as has been reported in several countries, and resistance may result in treatment failure.

Richard Winn, MD, MS, FCCP
Immediate Past Chair

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2. Pan American Health Organization/World Health Organization. Epidemiological Alert: Candida auris outbreaks in health care services. October 3, Washington, DC: PAHO/WHO; 2016.
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***EIC Search** continued from previous page*

mation in the way that our members and learners find the most accessible.

Question: Where do "we" want the journal to go?

Answer: Your leadership of the American College of Chest Physicians has great respect for the editorial independence of the journal. The EIC and the Editorial Board that is assembled will lead where the journal goes. As the embodiment of the brand of the CHEST organization, we clearly want to see the journal continue to be the authoritative, respected, trusted, "go to" resource for clinical pulmonary, critical care, and sleep medicine professionals.

CHEST is now accepting applications for the position of Editor in Chief of the *CHEST*® journal. For more information visit http://info.chestnet.org/editor-in-chief. Applications are due by February 1, 2018.

Congratulations, CHEST!

2017 Accreditation With Commendation

On December 2, CHEST received Accreditation with Commendation from the Accreditation Council for Continuing Medical Education (ACCME). This achievement grants CHEST accreditation through November 2023, and places the organization in the highest tier of continuing medical education (CME) providers.

"It is a true privilege to serve as a member of our outstanding CHEST Education team. We are very proud of our education program and have worked very hard to provide CHEST members and their health-care team with state-of-the-art learning opportunities," said Alex Niven, MD, FCCP, current Chair of CHEST's Education Committee, "ACCME Accreditation with Commendation is an important benchmark of this success, and we look forward to further advancing CHEST's leadership role in medical education through its simulation, active learning, and other innovative educational offerings."

To receive accreditation from the ACCME, CHEST met all of the requirements of the ACCME, has transitioned clinician knowledge into action, and has enhanced procedural performance to improve patient outcomes. Accreditation with Commendation is "a reward for going above and beyond requirements--having the absolute best practices and for striving to meet the aspirational goals of medical education," said William Kelly, MD, FCCP, previous Chair of CHEST's Education Committee.

In achieving Accreditation with Commendation, CHEST demonstrated compliance with the following:

- Improving the professional practice by consistently integrating CME into CHEST processes.
- Utilization of noneducation strategies such as the CHEST Foundation's grant programs and disease awareness campaigns, to enhance change as an adjunct to CHEST's activities/educational interventions.
- Identification of factors that effect patient outcomes and are outside of the provider's control.
- Implementation of educational strategies, including the offering of additional training to improve procedural capabilities, so as to remove, overcome, or address barriers to physician change.
- Building of bridges with stakeholders such as The France Foundation, National Comprehensive Cancer Network (NCCN), and the American Society for Clinical Pathology (ASCP), through collaboration and cooperation.
- Participation within an institutional framework for health-care quality improvement.
- Positioned to influence the scope and content of activities/educational interventions.

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1 Tapson, et al, "Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Submassive Pulmonary Embolism: OPTALYSE PE," American Thoracic Society (ATS) Meeting, Washington, DC, May 2017.

2 Lin, P., et al., "Comparison of Percutaneous Ultrasound-Accelerated Thrombolysis versus Catheter-Directed Thrombolysis in Patients with Acute Massive Pulmonary Embolism." *Vascular*, Vol. 17, Suppl. 3, 2009, S137-S147.

3 Nykamp M., et al. "Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemodynamic instability." *J Vascular Surgery: Venous and Lymphatic Disorders* 2015; 3(5): 251-7.

4 Piazza, G., et al., A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: the Seattle II study." *Journal of the American College of Cardiology: Cardiovascular Interventions* 2015; 8: 1382-92.

5 Acute efficacy pending long-term data availability for OPTALYSE PE.

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Imagine where we can go.

BTG