VOL. 14 • NO. 3 • MARCH 2019

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Bruce Jancin/MDedge News

Speaking at the Annual Cardiovascular Conference, Dr. Patrick T. O'Gara said, "Is aspirin safe and effective for primary prevention? The short answer here is no."

Aspirin for primary cardiovascular prevention: RIP

BY BRUCE JANCIN
MDedge News

SNOWMASS, COLO. – The decades-long belief that aspirin is beneficial for primary prevention of cardiovascular events was utterly dashed by three major randomized clinical trials during the space of a few short weeks in autumn 2018.

"Is aspirin safe and effective for primary prevention? The short answer here is no," Patrick T. O'Gara, MD, declared at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.

"Think of all those decades of aspirin therapy in the hopes of making ourselves healthier," added Dr. O'Gara, professor of medicine at Harvard Medical School, Boston, and a past president of the American College of Cardiology.

He cited the results of three placebo-controlled randomized trials totaling more than 47,000 patients without known cardiovascular disease: ARRIVE, published in late September 2018, followed in October by ASPREE and ASCEND.

• **ARRIVE.** This double-blind study conducted in seven countries included 12,546 patients deemed at moderate cardiovascular risk, with an estimated 10-year cardiovascular event risk of 17%. Eligibility was restricted to men aged 55 and up and women aged 60 or older. After a median follow-up of 5 years, there was no difference between patients assigned to enteric-coated

ASPIRIN // *continued on page 6*

E-cig use undoes gains of tobacco control in youth

BY HEIDI SPLETE
MDedge News

A significant increase during 2017-2018 in e-cigarette use among U.S. youths has erased recent progress in reducing overall tobacco product use in this age group, a study from the Centers for Disease Control and Prevention has found.

Nearly 5 million middle school and high school students in the United States, approximately 27% of high school students and 7% of middle school students, used tobacco products, including e-cigarettes, in 2018, according to study findings.

E-cigarettes are driving the trend. About 4 million high school students in the United States reported using any tobacco product in the last 30 days, and 3 million of them reported using e-cigarettes, according to a Vital Signs document published by the CDC on Feb. 11 in its Morbidity and Mortality Weekly Report.

In addition, many high school students who use e-cigarettes use them often; 28% reported using the products at least 20 times in the past 28 days, up from 20% in 2017.

"Any use of any tobacco product is unsafe for teens," Anne Schuchat, MD, principal deputy

E-CIGARETTES // *continued on page 4*

INSIDE HIGHLIGHT

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Phrenic nerve stimulation for treatment of central sleep apnea

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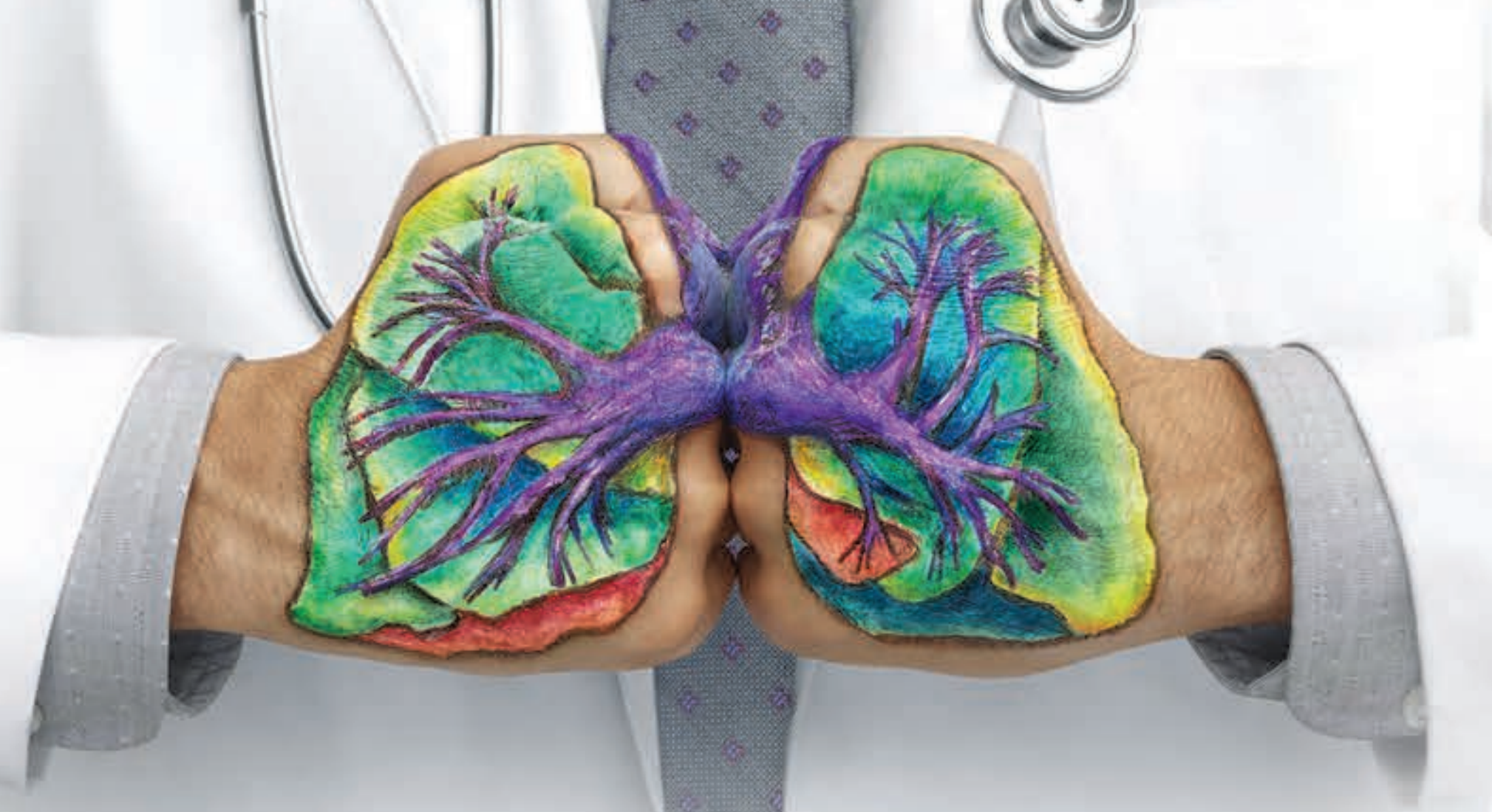

Indication

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

Select Important Safety Information

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

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

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

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

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

Drug Interactions:

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

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

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

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

Specific Populations:

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

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

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WE WON'T BACK DOWN FROM IPF

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

STUDIED IN A RANGE OF PATIENTS

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

DEMONSTRATED EFFICACY

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

ESTABLISHED SAFETY AND TOLERABILITY

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

COMMITTED TO PATIENTS

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

WORLDWIDE PATIENT EXPERIENCE

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

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

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

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

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

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

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

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

IPF=idiopathic pulmonary fibrosis.

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

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

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

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

Esbriet®
(pirfenidone) tablets 267 mg 801 mg

Marketing to teens coincided with jump in e-cigarette use // *continued from page 1*

director of the CDC, said in a teleconference to present the findings. Nicotine is highly addictive and can harm brain development in youth, including capacity for learning, memory, and attention, she said.

The rise in e-cigarette use corresponds with the rise in marketing and availability of e-cigarette devices such as JUUL, which dispense nicotine via liquid refill pods available in flavors including strawberry and cotton candy, said Brian King, MPH, PhD, deputy director for research translation at the CDC's Office on Smoking and Health.

"The advertising will lead a horse to water, the flavors will make them drink, and the nicotine will keep them coming back for more," said Dr. King.

Approximately 27.1% of high school students and 7.2% of middle school students used a tobacco product in 2018, a significant increase from 2017 data and with a major increase in e-cigarette use.

No change was noted in the use of other tobacco products, including cigarettes, from 2017 to 2018, according to the report. However, conventional cigarettes remained the most common companion product to e-cigarettes for

youth who use two or more tobacco products (two in five high school students and one in three middle school students in 2018). From a demographic standpoint, e-cigarette use was highest among males, whites, and high school students.

Tobacco use in teens is trending in the direction of wiping out the progress made in recent years to reduce exposure to youths. The report noted, "The prevalence of e-cigarette use by U.S. high school students had peaked in 2015 before declining by 29% during 2015-2016 (from 16% to 11.3%); this decline was the first ever recorded for e-cigarette use among youths in the National Youth Tobacco Survey since monitoring began, and it was subsequently sustained during 2016-2017). However, current e-cigarette use increased by 77.8% among high school students and 48.5% among middle school students during 2017-2018, erasing the progress in reducing e-cigarette use, as well as any tobacco product use, that had occurred in prior years."

The CDC and the Food and Drug Administration are taking action to curb the rise in e-cigarette use in youth in particular by seeking regulations to make the products less accessible, raising prices, and banning most flavorings, said Dr. Schuchat.

"We have targeted companies engaged in kid friendly marketing," said Mitch Zeller, JD, director of the Center for Tobacco Products for the FDA.

In a statement published simultaneously with the Vital Signs study, FDA Commissioner Scott Gottlieb, MD, emphasized the link between e-cigarette use in teens and the potential for future tobacco use. "The kids using e-cigarettes are children who rejected conventional cigarettes, but don't see the same stigma associated with the use of e-cigarettes. But now, having become exposed to nicotine through e-cigs, they will be more likely to smoke." Dr. Gottlieb declared, "I will not allow a generation of children to become addicted to nicotine through e-cigarettes. We must stop the trends of youth e-cigarette use from continuing to build and will take whatever action is necessary to ensure these kids don't become future smokers." He reviewed steps taken in the past year by the FDA to counter tobacco use in teens but he warned of future actions that may need to be taken: "If these youth use trends continue, we'll be forced to consider regulatory steps that could constrain or even foreclose the opportunities for currently addicted adult smokers to have the same level of access to these products that they now enjoy. I recognize that such a move could come with significant impacts to adult smokers."

Parents, teachers, community leaders, and health care providers are on the front lines and can make a difference in protecting youth and curbing nicotine use, Dr. King said.

Although there are no currently approved medications to treat nicotine addiction in youth, research suggests that behavioral counseling, as well as reinforcement of the danger of nicotine from parents and other people of influence, can help, Dr. King said.

The Vital Signs report is based on data from the 2011-2018 National Youth Tobacco Survey, which assesses current use of cigarettes, cigars, smokeless tobacco, e-cigarettes, hookahs, pipe tobacco, and bidis among a nationally representative sample of middle and high school students in the United States. The findings were analyzed by the CDC, FDA, and the National Cancer Institute.

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SOURCE: Gentzke AS et al. MMWR. 2019 Feb 11. doi: 10.15585/mmwr.mm6806e1.

Aspirin raises bleeding risk // *continued from page 1*

aspirin at 100 mg/day versus placebo in the incidence of major adverse cardiovascular events, with a hazard ratio of 0.96. However, GI bleeding events were 2.1-fold more common in the aspirin group (Lancet. 2018 Sep 22;392[10152]:1036-46).

• **ASPREE.** This double-blind trial, conducted in Australia and the United States, included 19,114 community-dwelling participants aged 70 years or older, or 65 years or older for Hispanics and blacks in the United States. After a median 4.7 years of follow-up, there was no difference in major adverse cardiovascular events between subjects randomized to 100 mg/day of enteric-coated aspirin and those on placebo. So, as in ARRIVE, no benefit. However, the rate of major hemorrhage was 38% greater in the aspirin group (N Engl J Med. 2018 Oct 18;379[16]:1509-18).

Moreover, the rate of all-cause mortality was 14% greater in the aspirin group, a statistically significant difference, compared with controls. Drilling down, the investigators showed that the major contributor to this excess mortality in the aspirin group was their 31% greater rate of cancer-related death (N Engl J Med. 2018 Oct 18;379[16]:1519-28).

"Remember, we used to think that taking aspirin reduced the incidence of GI cancer, and, in particular, colon adenocarcinoma? Well, here's a very startling observation in 19,114 healthy elderly patients showing an increase in cancer-associated death with the use of aspirin," commented Dr. O'Gara.

• **ASCEND.** This study randomized 15,480 subjects with diabetes but no known cardiovascular disease to 100 mg/day of aspirin or placebo and followed them for a mean of 7.4 years. There was a significant 12% relative risk reduction in the composite endpoint of serious vascular events in the aspirin group; however, the aspirin-treated patients also had a 29% greater rate of major bleeding events (N Engl J Med. 2018 Oct 18;379[16]:1529-39).

"So in dealing with our diabetic patients, we could perhaps say there is a small reduction in the risk of cardiovascular outcomes that is overwhelmed by more than a factor of two with regard to an increase in the risk of bleeding," the cardiologist observed.

How did physicians get the aspirin story for primary prevention so wrong for so long? Dr. O'Gara pointed to the Physicians' Health Study, conducted mainly back in the 1970s, as one of the benchmark studies that led to the widespread use of aspirin in this way.

"I think the aspirin story has now been put into sharp focus just within the course of the last 6 months and should force all of us to reassess what it is that we advise patients," he concluded.

"I no longer reflexively give aspirin to, say, a 60-year-old with a calcium score of 200. I will give a statin."

Dr. O'Gara's presentation was the talk of the meeting, as many attendees hadn't yet caught up with the latest aspirin data.

During an Q&A session, Robert A. Vogel, MD, a preventive cardiology authority at the University of Colorado, Denver, was asked, given the new emphasis placed upon coronary artery calcium as a supplemental risk assessment tool in the latest guidelines, at what magnitude of coronary artery calcium score in a patient with no history of coronary disease he would give aspirin for secondary prevention.

"I know I don't know the answer to that question," Dr. Vogel replied. "I no longer reflexively give aspirin to, say, a 60-year-old with a calcium score of 200. I will give a statin. Statins in my book are so effective and safe that my threshold for giving a statin in a 60-year-old is virtually nothing. But with a calcium score of 2,000 or 5,000, I worry just like you worry."

He noted that the primary prevention patients in the three recent major trials were mostly 60-70 years of age or older. It's safe to assume that by that point in life many of them had silent atherosclerosis and would have had a non-zero coronary artery calcium score, had they been tested. And yet, aspirin didn't provide any net benefit in those groups, unlike the drug's rock-solid proven value in patients who have actually experienced a cardiovascular event.

Dr. O'Gara reported receiving funding from the National Heart, Lung and Blood Institute, from the National Institute of Dental and Craniofacial Research, from Medtronic in conjunction with the ongoing pivotal APOLLO transcatheter mitral valve replacement trial, and from Edwards Lifesciences for the ongoing EARLY TAVR trial.

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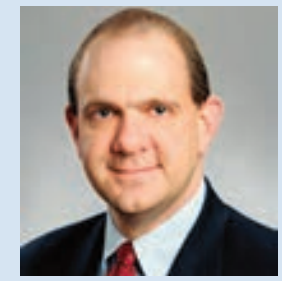

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CHEST PHYSICIAN (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is $244.00 per year. Phone 973-206-3434,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

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Shifting drugs from Part B to Part D: Costly to patients

BY GREGORY TWACHTMAN
MDedge News

A shift in Medicare drug coverage from Part B to Part D might save the government some money but could end up costing some patients in the long run.

Analysis of the 75 brand-name drugs with the highest Part B expenditures ($21.6 billion annually at 2018 prices) indicated that the government could save between $17.6 billion and $20.1 billion after rebates by switching coverage to Part D, Thomas J. Hwang of Harvard Medical School, Boston, and his associates said.

The potential for greater overall savings, however, "was constrained by the fact that 33 (44%) of the studied brand-name drugs were in protected classes, which HHS has reported precludes meaningful price negotiation by Part D plans," they wrote.

The proposal also could have a "material impact" on patient out-of-pocket costs, although the impact would vary based on the drug as well as patients' insurance coverage in addition to Medicare (JAMA Int Med. 2019. doi: 10.1001/jamainternmed.2018.6417).

For example, moving drug coverage to Part D would lower out-of-pocket costs for the majority of the 75 drugs for patients with Medigap supplemental insurance, but out-of-pocket costs could go up for almost 40% of products. Patients who would benefit most from the shift would be those who qualify for the low-income subsidy, which can eliminate coinsurance requirements.

DYNAMIC GRAPHICS/THINKSTOCK

"By contrast, for patients with Medigap insurance, out-of-pocket costs in Part D were estimated to exceed the annual premium costs for supplemental insurance [approximately 47-56 of the 75 drugs]," Mr. Hwang and his colleagues added. "Out-of-pocket costs would be increased under the proposed policy for beneficiaries with Medigap but without Part D coverage."

The analysis was limited by the inability to predict the proposed transition's impact on insurance premiums or drug utilization. Patients who were dually eligible for Medicare and Medicaid were excluded.

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SOURCE: Hwang TJ et al. JAMA Int Med. 2019. doi: 10.1001/jamainternmed.2018.6417.

VIEW ON THE NEWS

Transition must be carefully evaluated

Policy analysts need to be careful and do their due diligence to ensure all consequences of the policy options are fully understood, especially as pharmaceuticals account for greater costs in the Medicare program. Future policy analyses must, like Mr. Hwang and his associates did, account for changes to Medicare costs as well as beneficiary costs to understand the overall effects of policy changes.

Francis Crosson, MD, chairman of the Medicare Payment Advisory Commission, and Jon Christianson, PhD, vice chairman of MedPAC, made these comments in an accompanying editorial (JAMA Int Med. doi: 10.1001/jamainternmed.2018.6146).

ONC aims to help physicians, patients with information sharing in proposed rule

BY GREGORY TWACHTMAN
MDedge News

The Office of the National Coordinator of Health Information Technology is looking to adopt standardized application programming interfaces (APIs) in an effort to boost interoperability of health data.

The Department of Health & Human Services office posted a proposed rule Feb. 11 that would, according to an agency press release, "help allow individuals to securely and easily access structured and unstructured EHI [electronic health information] formats using smartphones and other mobile devices."

"We think our rule is going to help reduce burden and improve care," Michael Lipinski, director of the Regulatory Affairs Division in the ONC Office of Policy, said in an interview. "It is going to do that through technology. With the APIs, you should be able to get to your information easier and have it readily available. Whether that is from another health care provider or using other health care products through the API to improve care, you will have that ability between the certified API and the information blocking policies to use third party developers and their products."

The proposed rule also included a requirement that EHRs certified by ONC be able to easily export information contained within the EHR and make the format used to extract and export the data contained within the EHR publicly available.

"Another third-party developer can build to that and offer competing services to pull that information out," Mr. Lipinski said. "That would obviously help if you were choosing to switch [EHRs] if you didn't like the features you were getting from your EHR."

The standardizing of APIs to help the delivery of data will go hand in hand with information-blocking aspects of the proposed rule, which defines the few exceptions where an activity would not be considered information blocking, such as when engaging in practices will prevent patient harm; engaging in consistent, nondiscriminatory practices to protect patient privacy; and implementing practices to promote the security of health information.

Mr. Lipinski said these changes will help prevent providers from hiding behind HIPAA rules as the excuse to not share patient information, which will help with care coordination.

"From a provider's perspective, this should help them get more access to information, more access in a structured way and then easily get and share that information."

Ultimately, Mr. Lipinski said, the goal is "to increase competition and lower cost while still improving the quality of care for patients."

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PANDPSTOCK001/THINKSTOCK

Evaluate projects, not people, to address gender bias in research funding

BY SARA FREEMAN
MDedge News

LONDON – Female investigators are less likely to secure research funding than male investigators, not because their proposed project is of lesser scientific merit, but simply because they are women, according to research published in The Lancet.

Women had a 30% lower chance of success in getting funding for a project than did their male counterparts when the caliber of the principal investigator was considered as an explicit part of the grant application process, with an 8.8% probability of getting funded versus 12.7%, respectively. If the application was considered solely on a project basis, however, the gender bias was less (12.1% vs. 12.9%).

The overall success of grant applications was 15.8% in the analysis, which considered almost 24,000 grant applications from more than 7,000 principal investigators submitted to the Canadian Institutes of Health Research (CIHR) between 2011 and 2016.

"I see our study as basically one good thwack in a long game of whack-a-mole," lead study author Holly O. Witteman, PhD, said during an event to launch a special edition of The Lancet focusing on advancing women in science, medicine, and global health.

Dr. Witteman's research is one of three original articles included in the thematic issue that brings together female authors and commentators to look at gender equity and what needs to be done to address imbalances. The issue is the result of a call for papers that led to more than 300 submissions from more than 40 countries and, according to an editorial from The Lancet, highlights that gender equity in medicine "is not only a matter of justice and rights, it is crucial for producing the best research and providing the best care to patients."

That there are discrepancies in research funding awarded to female and male investigators has been known for years, Dr. Witteman, associate professor of family and emergency medicine at Laval University, Quebec City, said at the London press conference. To learn how and why, a "quasiexperimental" approach was used to find out what factors might be influencing the gender gap.

"Women are scored lower for competence compared to men with the same publication record," she said. It's not that they publish less or do easier research, or that the quality is lower, they are just viewed less favorably overall throughout their careers. Even when you control for confounding factors, "they still don't advance as quickly," she said.

"It had been documented for a while that, overall, women tend to get less grant funding and there hasn't been any evidence to show either way if maybe women's grant applications weren't as good," Dr. Witteman explained.

In 2014, the CIHR changed the way it funded research projects, creating a "natural experiment." Two new grant application programs were put in place which largely differed by whether or not an explicit review of the principal investigator and their ability to conduct the research was included.

SARA FREEMAN/MDEDGE NEWS

Dr. Holly O. Witteman: "It had been documented for awhile that, overall, women tend to get less grant funding and there hasn't been any evidence to show either way if maybe women's grant applications weren't as good."

Adjusting for age and type of research, Dr. Witteman and her coauthors found that there was little difference in the success of women in securing research funding when their grant applications were judged solely on a scientific basis; however, when the focus was placed on the principal investigator, women were disadvantaged.

Dr. Witteman said that "this provides robust evidence in support of the idea that women write equally good grant applications but aren't evaluated as being equally good scientists."

So how to redress the balance? Dr. Witteman suggested that one way was for funders to collect robust evidence on the success of grant applications and be transparent who is getting funded and how much funding is being awarded. Institutions should invest in and support young investigators, distributing power and flattening traditionally male-led hierarchies. Salaries should be aligned and research support evened out, she said.

Investigators themselves also have a role to play to do the best possible work and try to change the system. "Advocate for others," she said. That included advocating for others in groups that you may not be part of – which can be easier in some respects than advocating for a group that you are in.

"Funders should evaluate projects, not people," Jennifer L. Raymond, PhD, and Miriam B. Goodman, PhD, both professors at Stanford (Calif.) University wrote in a comment in The Lancet special issue. They suggested that people-based funding had been gaining popularity but that funders would be better off funding by project to achieve scientific and clinical goals. "Assess the investigator only after double-blind review of the proposed research is complete," they suggested. "Reduce the assessment of the investigator to a binary judgment of whether or not the investigator has the expertise and resources needed do the proposed research."

During a panel discussion at The Lancet event, Cassidy R. Sugimoto, PhD, associate professor of informatics at Indiana University in Bloomington and a program director for the Science and Innovation Policy Program at the National Science Foundation (NSF) observed that data on gender equality in research funding were already being collected and will be used to determine how best to adjust funding policies.

"Looking from the 1980s to the present, women make up shy of 20% of the funds given by the National Science Foundation," Dr. Sugimoto said. "That's improved over time, and it's at 28% currently, which is less than their authorship."

Tammy Clifford, PhD, vice president of research programs at the CIHR observed that data collection was "a critically important step, but of course that's not the only step," she said. "We need to look at and analyze the data regularly, and then when you see things that are not on track, you make changes."

One of the changes the CIHR has made is to train people who are reviewing grant applications on factors that may unconsciously affect their decisions. "There are things to be done, and I don't think we are quite there yet, but we are committed to continually looking at those data, to making the changes that are required."

Representing the Wellcome Trust, Ed Whiting, director of policy and chief of staff, said that the funding of projects led by female investigators was moving in the right direction. He noted that there was still a lower rate of applications from women for senior award levels, but that the panels that decide upon the funding were moving toward equal gender representation. The aim was to get to a 50/50 female-to-male ratio on the panels by 2020, he said; it is was at 46/52 in 2018.

Dr. Witteman and all other commentators had no financial disclosures.

SOURCE: Witteman HO et al. Lancet. 2019. doi: 10.1016/S0140-6736(18)32611-4.

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ALA report: Federal and state actions to limit tobacco use fall short

BY THERESE BORDEN
MDedge News

Tobacco use is currently at an all-time low thanks to public and private efforts, but more aggressive action from federal, state, and local governments is needed to protect the public, according to a review of tobacco control trends in the United States.

The American Lung Association (ALA) released "State of Tobacco Control" 2019, its 17th annual state-by-state analysis and list of recommended policy priorities to limit tobacco use. Although the report notes some positive steps taken by the federal and state governments, shortfalls in policy and legislation also are highlighted. The report states, "We know how and are ready to save more lives, but we need our elected officials to do much more. To many, solving America's tobacco crisis might seem like a complex puzzle with no solution. And yet we have known for years what pieces are needed to reduce the disease and death caused by tobacco use."

In this report, the federal government and each state are graded on a scale, A through F, for policy actions and laws to limit tobacco use. The grading methodology is based on a detailed point system cataloging the implementation and strength of specific actions and policies to limit tobacco use.

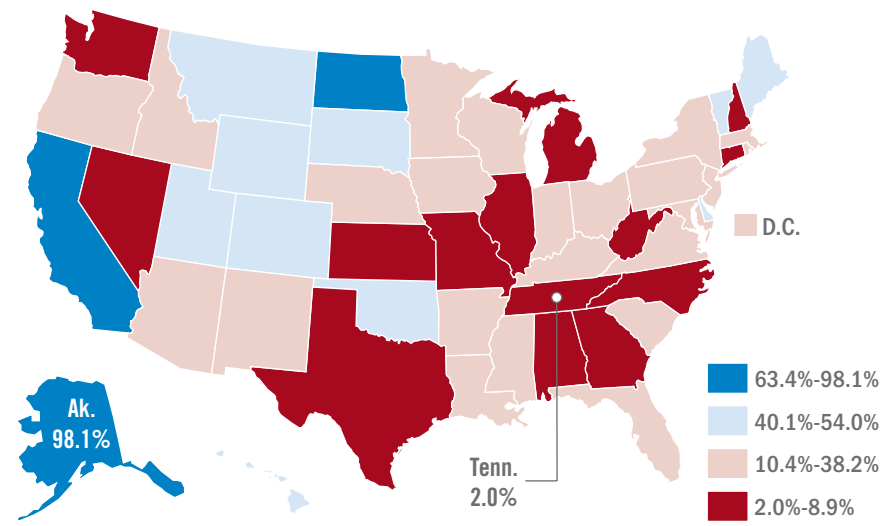
Areas of impact

The report focused on six areas of public policy that affect exposure to and use of tobacco:

- **Smoke-free air:** Protecting the public from secondhand smoke should be a priority for policymakers, according the report, but 22 states have no smoke-free workplace laws in place. Laws restricting e-cigarettes in workplaces and public buildings have lagged behind tobacco laws in many states.
- **Tobacco prevention funding:** Dedicated funds to prevent tobacco addiction before it starts is a key element of a public health attack on tobacco use, but no U.S. state currently spends what the Centers for Disease Control and Prevention has recommended. Twenty years ago, the Master Settlement Agreement between the tobacco industry and 46 states and the District of Columbia guaranteed ongoing payments to the states to be used for tobacco prevention and control. Although those funds have been collected in the states to the tune of $27 billion since 1998, overall only 2.4% of those funds have been spent for this purpose, and the rest has been budgeted for other purposes.
- **Tobacco taxes:** Sales taxes on tobacco products have been highly effective in preventing young people from taking up tobacco use, but those taxation rates have remained unchanged in 2018 in all but the District of Columbia and Oklahoma.
- **Tobacco 21:** "Increasing the legal age of sale for tobacco products to 21 would decrease tobacco use by 12% and could prevent 223,000 deaths among those born between 2000 and 2019," the report noted, citing a 2015 report by the Institute of Medicine. So far, the this restriction has been legislated in six states, the District of Columbia, and numerous local governments. The ALA considers increasing the age for tobacco sales to 21 to be a public health priority.
- **Helping smokers quit:** The report notes that current law requires that Medicaid expansion health plans and private insurance plans cover comprehensive smoking-cessation treatment. However, not all states have the expanded Medicaid program, and many of those with Medicaid expansion don't offer coverage of all Food and Drug Administration–approved cessation treatments. Despite laws requiring smoking cessation coverage, many private insurance plans still do not include this coverage. The ALA recommends enforcement of the current law with regard to tobacco-cessation insurance coverage.
- **FDA regulation of tobacco products:** The FDA has announced plans to make a major effort to reduce tobacco use in young people, decrease nicotine in cigarettes, and restrict flavored tobacco products. But these plans fall short of the aggressive action needed to curb the tobacco "epidemic," according to the report. Delayed action and timid policy have "resulted in tobacco companies becoming more emboldened to devise new and egregious ways to addict youth and sustain addiction among current users." The ALA report points to the steep rise in e-cigarette use among youth with a 20.8% rise in high school students using these products in 2018, a rise from 11.7% in 2017. This trend is not likely to be reversed by the FDA proposals to date, which rely on voluntary action by the industry to curb youth use, sales restrictions to youth, and restrictions on some flavored tobacco products.

State spending on tobacco prevention for fiscal year 2019

Proportion of CDC-recommended level



Note: Based on state revenue data from the Campaign for Tobacco-Free Kids.
Source: American Lung Association

The report card

Federal government efforts in regulation of tobacco products, taxation, and health insurance coverage of cessation all received an F in this report, while mass media campaigns were given an A.

The states didn't fare much better. They were graded on prevention and control funding, smoke-free air, taxation, access to cessation services, and minimum age for sales. A total of 19 states received a grade of F in four or five of these areas.

Funding for prevention and control was evaluated as the percentage of the amount recommended by the CDC, adjusted for a variety of state-specific factors such as prevalence of tobacco use, cost and complexity of conducting mass media campaigns, and proportion of the audience below 200% of the federal poverty level. A limitation of this methodology of grading funding is that it doesn't evaluate effectiveness of the spending or the level of spending in different program categories. The higher spenders on prevention and control were Alaska at 98.1% and California at 74.5% of the CDC recommended level. The lowest spenders were Tennessee at 2.0% and Missouri at 3.0%.

All but eight states received an F on minimum age for tobacco sales because most have an age limit 18 instead of the ALA and CDC recommendation of age 21.

Harold Wimmer, the CEO of the American Lung Association, wrote, "Aggressive action by our country's federal and state policymakers is urgently required. However, 'State of Tobacco Control' 2019 has found a disturbing failure by federal and state governments to take action to put in place meaningful and proven-effective policies that would have prevented, and reduced tobacco use during 2018. This failure to act places the lung health and lives of Americans at risk. We have also found that this lack of action has emboldened tobacco companies to be even more brazen in producing and marketing products squarely aimed at kids, such as the JUUL e-cigarettes that look like an easily concealed USB drive, which now dominate the market driven by youth use."

The full report is available for download at the ALA website.

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SOURCE: American Lung Association, "State of Tobacco Control 2019."

Benralizumab effective for severe asthma at 2 years

BY JIM KLING
MDedge News

Benralizumab is safe and effective for the treatment of uncontrolled asthma out to 2 years, according findings of the BORA trial, an extension study of the phase 3 SIROCCO and CALIMA trials. The study follows up and reinforces previously reported 1-year data and was reported by William W. Busse, MD, of University of Wisconsin, Madison, and his colleagues in the Lancet Respiratory Medicine.

Benralizumab is a monoclonal antibody that targets interleukin-5 receptor alpha. It causes rapid deletion of eosinophils through cell-mediated cytotoxicity. A 30-mg dose of benralizumab every 8 weeks is approved for severe asthma treatment in the United States, and other countries.

In the second year, there were no new adverse events associated with depleted eosinophils, and the frequency of opportunistic infections was similar to the first year.

The 48-week SIROCCO trial, the 56-week CALIMA trial, and the 28-week ZONDA trial tested the effect of benralizumab 30 mg given every 4 weeks or 8 weeks, combined with high-dosage inhaled steroids and long-acting beta$_2$-agonists. The 8-week dose of the drug reduced annual exacerbations by 51%, compared with placebo in the SIROCCO trial and by 28% in the CALIMA trial. In the ZONDA trial, benralizumab reduced oral glucocorticoid use by 75%, compared with placebo, and by 25% from baseline.

The BORA extension trial included participants in the previous three trials. In the current report, researchers presented results from the analysis from BORA participants recruited from the SIROCCO and CALIMA trials. Data from participants from all three trials will be reported in the future.

The analysis included 1,576 patients who continued to receive benralizumab after being assigned to the treatment arm in SIROCCO or CALIMA, or who had received placebo and then were randomized to benralizumab on the 4-week (n = 783; 265 from placebo) or 8-week dose (n = 793; 281 from placebo) schedule.

A total of 166 patients, or about 10% in each group, discontinued treatment. The frequency of any serious adverse event (SAE) ranged between 10% and 11% in all groups. SAEs associated with infections ranged from 1% to 3%, indicating that there were no significant differences in SAE frequencies between those who were originally assigned to placebo and those who originally received benralizumab. That suggests no safety differences between receiving the drug for 1 year or 2 years.

AstraZeneca and Kyowa Hakko Kirin funded the studies. The authors have received fees from AstraZeneca and other pharmaceutical companies, and some are employees of AstraZeneca.

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SOURCE: Busse WW et al. Lancet Respir Med. 2019 Jan 1;7(1):46-59.

E-cigarettes beat nicotine patch but quit rates still low

BY ANDREW BOWSER
MDedge News

E-cigarettes might be more effective for smoking cessation than nicotine replacement therapy, results of a randomized study of almost 900 adults suggest.

Rates of abstinence at 1 year were 18% for adults who used refillable e-cigarettes to wean themselves off smoking, according to the reported results, compared with about 10% for those who tried nicotine replacement therapies.

"This is particularly noteworthy given that nicotine replacement was used under expert guidance, with access to the full range of nicotine replacement products, and with 88.1% of participants using combination treatments," said investigator Peter Hajek, PhD, of Queen Mary University of London, and his coauthors in the New England Journal of Medicine.

The findings contrast with those of earlier studies, which showed a lesser effect of e-cigarettes as a stop-smoking strategy, Dr. Hajek and coauthors wrote.

In previous studies, participants used first-generation cartridge-based e-cigarettes, while in the present study, they were given second-generation refillable e-cigarettes and free choice of e-liquids, the authors noted. Moreover, those previous studies provided limited face-to-face support, they said, but this study included weekly behavioral support for at least 4 weeks in both the e-cigarette and nicotine replacement groups.

The randomized study by Dr. Hajek and his colleagues included 886 adults in the United Kingdom attending stop-smoking services provided by the U.K. National Health Service. They were randomized to receive either an e-cigarette starter pack and one bottle of nicotine-containing e-liquid, or 3 months' worth of nicotine replacement products of their own choosing. At the 52-week validation visits, the study participants received about the equivalence of about $26 U.S. dollars for their travel and time.

Abstinence from smoking at 52 weeks, which was verified by measuring expired carbon monoxide levels, was achieved in 18.0% of the e-cigarette group and 9.9% of the nicotine replacement group (relative risk, 1.83; 95% confidence interval, 1.30-2.58; *P* less than .001), according to the report.

However, the rate of continued e-cigarette use was "fairly high," investigators wrote. Eighty percent of the e-cigarette group was still using their assigned product at 52 weeks, compared with just 9% in the nicotine replacement group.

"This can be seen as problematic if e-cigarette use for a year signals long-term use, which may pose as-yet-unknown health risks," they said.

Tobacco withdrawal symptoms were less severe and satisfaction ratings were higher with e-cigarettes versus nicotine replacement therapy, similar to what had been observed in previous studies, investigators said.

They cited several limitations. For example, product assignments were not blinded. However, the investigators said they tried to "limit expectation effects by recruiting only participants with no strong product preference."

Dr. Hajek reported grants and fees from Pfizer unrelated to the present study. Coauthors reported disclosures related to Pfizer and Johnson and Johnson, along with grants from the U.K. National Institute for Health Research.

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SOURCE: Hajek P et al. N Engl J Med. 2019;380:629-37. doi: 10.1056/NEJMoa1808779.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Cessation success rates are low in both the e-cigarette group and the nicotine replacement group. "Cessation" in the e-cigarette group meant the group quit traditional cigarettes; most of the quitters were still using e-cigarettes. Maybe e-cigarettes have a role in tobacco cessation. Maybe. That doesn't mean that they are healthy or safe.

Immunotherapy's cardiac effects require early monitoring, management

BY NEIL OSTERWEIL
MDedge News

WASHINGTON – Unquestionably, immunotherapy is revolutionizing the care of patients with various solid tumors such as lung cancer and hematologic malignancies.

But it's equally true that there's no such thing as either a free lunch or a cancer therapy free of side effects, whether it's increased risk for heart failure associated with anthracycline-based chemotherapy, or inflammatory conditions, arrhythmias, and thromboembolic events associated with immune checkpoint inhibitors, said R. Frank Cornell, MD, of Vanderbilt University Medical Center in Nashville, Tenn.

"Early awareness and intervention is critical for improved outcomes, and a multidisciplinary approach between oncology, cardiology, the clinic nurse, and other health care providers is critical in managing these patients with these complicated therapies," he said at the American College of Cardiology's Advancing the Cardiovascular Care of the Oncology Patient meeting.

Checkpoint inhibitors and the heart

Toxicities associated with immune checkpoint inhibitors such as the programmed death 1/ligand 1 (PD-1/PD-L1) inhibitors nivolumab (Opdivo) and pembrolizumab (Keytruda) and the cytotoxic T-lymphocyte antigen 4 antibody ipilimumab (Yervoy) tend to mimic autoimmune conditions, Dr. Cornell said. All three of these agents are used to treat lung cancer and other cancers.

Cardiovascular events associated with these agents, while uncommon, include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis, and venous thromboembolism, he said, citing an American Society of Clinical Oncology (ASCO) clinical practice guideline (J Clin Oncol 2018;36[17]:1714-68).

Dr. Cornell described the case of a 63-year-old woman with disseminated metastatic melanoma who presented to the emergency department 10 days after starting on combination therapy with ipilimumab and nivolumab. She had developed shortness of breath, pleuritic chest pain, and a mild cough for 1 or 2 days.

Her cardiac laboratory markers had been normal at baseline, but were markedly elevated on presentation, and electrocardiograms showed complete heart block and subsequent ventricular tachycardia.

The patient was started on high-dose prednisone, but she died in hospital, and an autopsy showed that the cause of death was infiltration into the myocardium of CD3-positive and CD8-positive T lymphocytes.

"So how do we manage this? This is a good opportunity, I think, for further cardiology and oncology collaboration to develop more robust guidelines for what we can do to best prevent this," Dr. Cornell said.

Patients started on the ipilimumab/nivolumab combination should be tested weekly for cardiac troponin, creatine kinase (CK) and CK-muscle/brain (CK-MB) weekly for the first 3-4 weeks of therapy. Therapy should be stopped if troponin levels continue to rise, and the patient should be started on high-dose steroids, he said.

NEIL OSTERWEIL/MDEDGE NEWS

Dr. R. Frank Cornell said, "Early awareness and intervention is critical for improved outcomes, and a multidisciplinary approach between oncology, cardiology, the clinic nurse, and other health care providers is critical in managing these patients with these complicated therapies."

The role of other anti-inflammatory agents such as infliximab (Remicade and biosimilars) is unclear and needs further study, he added.

Dr. Cornell cited a 2018 letter to The Lancet by Javid J. Moslehi, MD, and colleagues from Vanderbilt describing an increase in reports of fatal myocarditis among patients treated with checkpoint inhibitors.

"We highlight the high mortality rate with severe immune checkpoint inhibitor–related myocarditis, which is more frequent with combination PD-1 and CTLA-4 blockade, but can also occur with monotherapy. Myocarditis was observed across immune checkpoint inhibitor regimens, although it remains too early to determine whether the incidence differs between use of anti-PD1 and anti-PD-L1 drugs. Furthermore, this condition occurs early on during therapy and across cancer types," they wrote.

Most of the patients had no preexisting cardiovascular disease, and most were not taking medications for hypertension, cardiovascular disease, or diabetes.

CAR-T cells and cardiac disease

The primary cardiac complications associated with CAR-T cell therapy are related to the cytokine release syndrome (CRS), a condition marked by progressive elevation in inflammatory cytokines that in turn leads to marked elevations in C-reactive protein (CRP), interferon gamma, tumor necrosis factor alpha, and release of pro-inflammatory cytokines including interleukin (IL)-6, IL-10, IL-12, and IL-1 beta.

In rare instances, CRS can lead to disseminated intravascular coagulation (DIC), capillary leak syndrome, and a hemophagocytic lymphohistiocytosis-like (HLH) syndrome, Dr. Cornell said.

Package inserts for the two Food and Drug Administration–approved CAR-T cell products, axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) show that each was associated in clinical trials with a high incidence of CRS.

Among patients treated with axicabtagene ciloleucel, 94% developed CRS, which was grade 3 or greater in severity in 13%. The median time to onset was 2 days, and the median duration was 7 days. Cardiovascular adverse events included grade 3 or greater tachycardia in 2%, arrhythmias in 7%, edema in 1%, dyspnea in 3%, pleural effusion in 2%, hypotension in 15%, hypertension in 6%, and thrombosis in 1%.

Among patients treated with tisagenlecleucel, 79% treated for B-cell acute lymphoblastic leukemia (B-ALL) and 74% treated for diffuse large B-cell lymphoma (DLBCL) developed CRS, which was grade 3 or greater in 49% and 23% of patients, respectively. The median time to onset was 3 days, and the median duration of CRS was 8 days.

Cardiovascular adverse events of grade 3 or greater among these patients included tachycardia in 4%, fluid overload in 7%, edema in 1%, dyspnea in 12%, pulmonary edema in 4%, hypotension in 22%, and hypertension in 6%.

Risk factors for CRS include high pre-infusion tumor burden, active infections, and concurrent inflammatory processes, Dr. Cornell said.

Prevention of cardiovascular complications of CAR-T cell therapy requires management of CRS. Patients with grade 2 or greater CRS should receive the anti–IL-6 agent tocilizumab (Actemra) 8 mg/kg intravenously over 1 hour to a maximum dose of 800 mg. Tocilizumab infusions can be repeated every 8 hours as needed if the patient is not responsive to intravenous fluids or increasing supplement oxygen, but should be limited to a maximum of three doses over 24 hours, and a maximum total of four doses.

Patients with grade 3 CRS should also receive intravenous methylprednisolone 1 mg/kg twice daily or the equivalent amount of dexamethasone, with corticosteroids continued until the severity of CRS is grade 1 or less, then tapered over 3 days,

Patients with grade 4 CRS should also receive IV methylprednisolone 1,000 mg per day for 3 days, and if symptoms improve, continue management as per grade 3, Dr. Cornell said.

Dr. Cornell reported having nothing to disclose.

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

POWER TO PREVENT EXACERBATIONS[1-3]

ACCORDING TO AN ANALYSIS OF NHANES DATA, 69% OF ADULT PATIENTS WITH ASTHMA HAD EOSINOPHILIC ASTHMA*[4]

GET STARTED AT FASENRAFACTS.COM

FASENRA is proven to reduce annual exacerbation rate in patients with severe eosinophilic asthma.[1-3]

NHANES=National Health and Nutrition Examination Survey.

*Data from the 2005 to 2006 annual survey of a nationally representative sample of a noninstitutionalized United States population in patients with asthma (aged 18-64 years) identified based on the participants' self-report. Eosinophilic asthma was defined as a blood eosinophil cutoff point of ≥150 cells/µL. Of the 310 adult patients, 69% had a blood eosinophil level ≥150 cells/µL.[4]

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.

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.

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

CHARACTERISTICS OF PATIENTS WITH ALLERGIC OR NONALLERGIC EOSINOPHILIC ASTHMA[5,6]:

Elevated level of blood eosinophils

AND/OR

Frequent exacerbations (≥2 exacerbations annually)

ICS at high doses are insufficient to control the disease

CHOOSE FASENRA FOR PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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.

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

FASENRA IS THE #1 RESPIRATORY BIOLOGIC

SELECTED BY PHYSICIANS FOR NEW PATIENTS IN SEVERE EOSINOPHILIC ASTHMA*[7]

*Data are not intended to suggest comparison of safety or efficacy to any other IL-5 or IL-5Rα treatment.[7]

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. Patients were stratified by geography, age, and blood eosinophil counts (≥300 cells/μL and <300 cells/μL). The primary endpoint was annual exacerbation rate ratio vs 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]

References: 1. FASENRA® (benralizumab) [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.** Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42. **5.** de Groot JC, ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1:1-11. **6.** de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res*. 2016;2(2):1-8. **7.** Data on File, US-22015, AZPLP.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

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

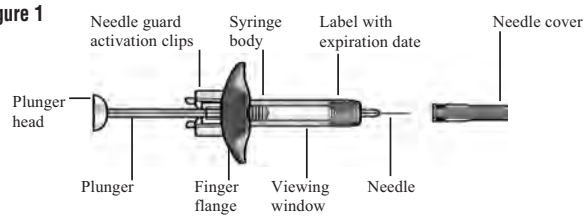
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

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.

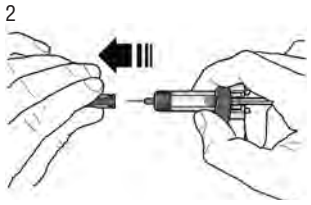
Figure 1



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]*.

Manufactured by
AstraZeneca AB
Södertälje, Sweden SE-15185
US License No. 2059

Distributed by
AstraZeneca Pharmaceuticals LP,
Wilmington, DE 19850

Iss. 11/17 US-12989 12/17

SGLT-2 inhibitors promising for heart failure prevention, not treatment

BY DOUG BRUNK
MDedge News

LOS ANGELES – Mounting evidence suggests that the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors helps prevent heart failure.

They also may play a role in the treatment of patients with known heart failure (HF), but further studies are required to prove definite treatment benefit.

"These trials enrolled a minority of patients with known heart failure, and, in those subgroups, the drugs seem to reduce the risk for hospitalization, opening the possibility of treatment benefit," Javed Butler, MD, said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease. "But there were not enough patients to conclude this. If you are treating diabetes with these agents in patients with heart failure, more power to you. But don't think you are treating heart failure per se until the results of the dedicated heart failure trials come out."

Good glycemic control has not been shown to affect heart failure outcomes per se, said Dr. Butler, professor and chairman of the department of medicine at the University of Mississippi Medical Center, Jackson.

"People seem to mix the concepts of prevention and treatment together," he said. "We have now very good evidence across all trials with SGLT-2 inhibitors for prevention of heart failure. But for treatment, we need more data despite favorable early signals.

"Also, these trials include most patients with ischemic heart disease, but we don't have data on nonischemic etiology for the development of heart failure from these trials," Dr. Butler added.

The best available data from clinical trials suggest that patients with American College of Cardiology Foundation/American Heart Association heart failure classification stages A and B benefit the most from aggressive treatment to prevent HF.

"Either they have diseases like high blood pressure or diabetes, but their hearts are normal, or, perhaps, their hearts are abnormal, and they develop left ventricular hypertrophy or atrial fibrillation," he said. "However, if someone is stage C – manifest heart failure – or stage D – advanced heart failure – we need further data on novel therapies to improve their outcomes."

Dr. Butler emphasized that not all heart failure is associated with atherosclerotic vascular disease. In fact, the Health, Aging, and Body Composition Study showed that the incidence of heart failure increased progressively across age groups, both for those with and without a preceding vascular event ($P = .03$ and P less than .001, respectively; Eur J Heart Fail. 2014 May;16[5]:526-34). "There's a whole other world of nonischemic heart failure that we also need to worry about," he said. "There is a lot of microvascular endothelial dysfunction."

Dr. Butler

The combination of heart failure and diabetes is especially lethal. "If you put them together, you're looking at about a 10-fold higher risk of mortality, which is a horrible prognosis," Dr. Butler said. "That means that we need to think about prevention and treatment separately."

Data from the SAVOR-TIMI 53, EXAMINE, and TECOS trials show there is no protective effect of dipeptidyl peptidase–4 inhibitors when it comes to hospitalization for heart failure.

"The other classes of drugs either increase the risk, or we don't have very good data," Dr. Butler said. "So far, across the spectrum of therapies for diabetes, the effect on heart failure is neutral and perhaps confers some risk."

SGLT-2 inhibitors convey a different story.

In the EMPA-REG OUTCOME trial, one inclusion criterion was established cardiovascular disease (CVD) in the form of a prior MI, coronary artery disease, stroke, unstable angina, or occlusive peripheral artery disease, but not heart failure alone (N Engl J Med. 2015 Nov 26; 373[22]:2117-28).

"This was not a heart failure study, so we don't know what their New York Heart Association class was, or the details of their baseline HF treatment in the minority of patients who were enrolled who had a history of HF," Dr. Butler cautioned.

However, the trial found that empagliflozin conferred an overall cardiovascular death risk reduction of 38%, compared with placebo.

When the researchers assessed the impact of treatment on all modes of cardiovascular death, they found that death from heart failure benefited the most (hazard ratio, 0.32; $P = .0008$), while sudden death benefited as well. Empagliflozin also had a significant impact on reduced hospitalization for heart failure, compared with placebo (HR, 0.65).

Empagliflozin conferred an overall cardiovascular death risk reduction of 38%, compared with placebo.

"This is a large enough cohort that you should feel comfortable that this drug is preventing heart failure in those with HF at baseline," said Dr. Butler, who was not involved with the study. "We can have a debate about whether this is a treatment for heart failure or not, but for prevention of heart failure, I feel comfortable that these drugs do that."

A subsequent study of canagliflozin and cardiovascular and renal events in type 2 diabetes showed the same result (N Engl J Med. 2017 Aug 17; 377[7]:644-57). It reduced hospitalization for heart failure by 33% (HR, 0.67).

Then came the CVD-REAL study, which found low rates of hospitalization for heart failure and all-cause death in new users of SGLT-2 inhibitors. More recently, DECLARE-TIMI 58 yielded similar results.

"One of the criticisms of these findings is that heart failure characteristics were not well phenotyped in these studies," Dr. Butler said. "I say it really does not matter. Heart failure hospitalizations are associated with a poor prognosis irrespective of whether the hospitalization occurred in patients without heart failure or in a patient with previously diagnosed heart failure, or whether the patient has reduced or preserved ejection fraction.

"Framingham and other classic studies show us that 5-year mortality for heart failure is about 50%," he noted. "If you can prevent a disease that has a 5-year mortality of 50%, doesn't that sound like a really good deal?"

A contemporary appraisal of the heart failure epidemic in Olmstead County, Minn., during 2000-2010 found that the mortality was 20.2% at 1 year after diagnosis, and 52.6% at 5 years after diagnosis. The data include new-onset HF in both inpatient and outpatient settings.

Specifically, new-onset HF hospitalization was associated with a 1-year postdischarge mortality of 21.1% (JAMA Intern Med. 2015;175[6]:996-1004).

"We cannot ignore prevention of heart failure," Dr. Butler said. "Also, for treatment, once you get hospitalized for heart failure, the fundamental natural history of the disease changes. There is a 30% cumulative incremental death risk between the second and third hospitalizations."

Dr. Butler concluded his presentation by noting that five randomized, controlled trials evaluating SGLT-2 inhibitors in HF have been launched, and should help elucidate any effects the drugs may have in treating the condition. They include EMPEROR-Preserved (NCT03057951), EMPEROR-Reduced (NCT03057977), Dapa-HF (NCT03036124), and SOLOIST-WHF (NCT03521934) and DELIVER (NCT03619213).

Dr. Butler disclosed that he has received research support from the National Institutes of Health, the European Union, and the Patient-Centered Outcomes Research Institute. He has also been a consultant for numerous pharmaceutical companies, including Boehringer Ingelheim, Janssen, and AstraZeneca, which sponsored the EMPA-REG, CANVAS, and DECLARE TIMI 58 trials.

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Revised U.S. A fib guidelines revamp anticoagulation

BY MITCHEL L. ZOLER
MDedge News

The first update to U.S. medical-society guidelines for managing atrial fibrillation since 2014 raised the threshold for starting anticoagulant therapy in women, pegged the direct-acting oral anticoagulants (DOACs) as preferred over warfarin, and introduced for the first time weight loss as an important intervention tool for treating patients with an atrial arrhythmia.

On Jan. 28, the American College of Cardiology, American Heart Association, and Heart Rhythm Society posted online a 2019 focused update (Circulation. 2019 Jan 28. doi: 10.1161/CIR.0000000000000665) to the 2014 atrial fibrillation (AF) management guidelines that the groups had previously published (J Am Coll Cardiol. 2014 Dec 2;64[21]:2246-80).

Perhaps the two most important changes, as well as the two that lead off the new document, were a pair of class I recommendations on using oral anticoagulation in AF patients.

One of these updates reset the threshold for initiating oral anticoagulant therapy in women from 2 points on the CHA2DS2-VASc scale to 3 points, while leaving the threshold for men unchanged at 2 points. This brought U.S. guidelines in line with European guidelines, set by the European Society of Cardiology in 2016 (Eur Heart J. 2016 Oct 7;37[38]:2893-962). It will now also mean that, because of the way the CHA2DS2-VASc score is calculated, women with AF who are at least 65 years old will no longer automatically get flagged as needing oral anticoagulant therapy.

"This is a really important shift. It's recognition that female sex is not as important a risk factor [for AF-associated stroke] as once was thought," commented Hugh Calkins, MD, professor of medicine at Johns Hopkins Medicine in Baltimore and a member of the panel that wrote the update. "This will change the number of women with AF who go on anticoagulation," predicted Dr. Calkins, who directs the cardiac arrhythmia service at his center.


Dr. Calkins

The second important change to the anticoagulation recommendations was to specify the DOACs as recommended over warfarin in AF patients eligible for oral anticoagulation and without moderate to severe mitral stenosis or a mechanical heart valve, which also matches the 2016 European guidelines and updates the prior, 2014, U.S. guidelines, which didn't even mention DOACs.

Prescribing a DOAC preferentially to AF patients has already become routine among electrophysiologists, but possibly not as routine among primary care physicians, so this change has the potential to shift practice, said Dr. Calkins. But the higher price for DOACs, compared with warfarin, can pose problems. "The cost of DOACs remains an issue that can be a serious limitation to some patients," said Craig T. January, MD, professor of medicine at the University of Wisconsin in Madison and chair of the guideline-writing panel.

Another notable change in the 2019 update was inclusion for the first time of weight loss as a recommended intervention, along with other risk factor modification, an addition that Dr. Calkins called "long overdue."

"This is a new recommendation, and it will potentially be important," said Dr. January, although the guidelines do not spell out how aggressive clinicians should be about having patients achieve weight loss, how much loss patients should achieve, or how they should do it. "There are a lot of observational data and basic science data suggesting the importance of weight loss. Most electrophysiologists already address weight loss. The problem is how to get patients to do it," commented Vivek Reddy, MD, professor of medicine and director of cardiac arrhythmia services at Mount Sinai Hospital in New York.

Dr. Reddy expressed surprise over two other features of the updated guidelines. For the first time, the guidelines now address percutaneous left atrial appendage (LAA) occlusion and say: "Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation." The guidelines' text acknowledges that this runs counter to the Food and Drug Administration labeling for the Watchman LAA occlusion device, which restricts the device to patients "deemed suitable for long-term warfarin (mirroring the inclusion criteria for enrollment in the clinical trials) but had an appropriate rationale to seek a nonpharmacological alternative to warfarin."


Dr. Reddy

"We do not take a position on the FDA's" actions, Dr. January said in an interview.

"The ACC, AHA, and HRS guidelines should reflect what the FDA decided," Dr. Reddy said in an interview. "I'm a little surprised the guidelines said that anticoagulation had to be contraindicated.

The 2019 update also added a class IIb, "may be reasonable" recommendation for catheter ablation of AF in patients with heart failure with reduced ejection fraction.

Dr. Calkins has been a consultant to Abbott, Altathera, AtriCare, Boehringer-Ingelheim, King, Medtronic, and St. Jude and has received research funding from Boehringer-Ingelheim, Boston Scientific, and St. Jude. Dr. January had no disclosures. Dr. Reddy has been a consultant to, received research funding from, or has an equity interest in more than three dozen companies.

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Medical advice can drive emergency visits by AF patients

BY MITCHEL L. ZOLER
MDedge News

BOSTON – Patients with atrial fibrillation who present to emergency departments, despite being asymptomatic, often go based on their understanding of advice they had previously received from their physicians, according to results from a prospective study of 356 Canadian atrial arrhythmia patients seen in emergency settings.


Dr. Glover

One way to deal with potentially inappropriate emergency department use is to have concerned patients with atrial fibrillation (AF) record their heart rhythm data with a handheld device or watch, transfer the records to their smartphones, and transmit the information to a remote physician for interpretation and advice, Benedict M. Glover, MD, said at the annual International AF Symposium.

Dr. Glover and his associates are in the process of developing a prototype system of this design to address the need they identified in a recent registry of 356 patients with a primary diagnosis of AF who sought care in the emergency department of any of seven participating Canadian medical centers, including five academic centers and two community hospitals. The survey results showed that 71% of the patients were symptomatic and 29% were asymptomatic then they first presented to an ED.

Case reviews of the 356 patients showed that 152 (43%) came to the EDs for what were classified as inappropriate reasons. The most common cause by far of an inappropriate ED presentation was prior medical advice the patient had received, cited in 62% of the inappropriate cases, compared with 9% of the appropriate cases, said Dr. Glover, an electrophysiologist at Sunnybrook Health Sciences Centre in Toronto.

The inappropriate ED use by AF patients could be addressed in at least two ways, he said. One solution might be to give patients an alternative destination, so that instead of going to an ED they could go to an outpatient AF clinic. A second solution is to give patients a way to have their heart rhythm assessed remotely at the time of their concern. Dr. Glover said that his center had the staff capacity to deal with the potential influx of rhythm data from a pilot-sized program of remote heart-rhythm monitoring, but he conceded that scaling up to deal with the data that could come from the entire panel of AF patients managed by Sunnybrook physicians would be a huge challenge.

Dr. Glover had no disclosures.

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THE GOLD 2019 REPORT

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- **Does not include ICS/LABA as initial treatment for many patients[1]**

ANORO was studied in patients with moderate or worse COPD.

ANORO is for the once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

ANORO is NOT for the relief of acute bronchospasm or for asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA.

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

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

START WITH ANORO FOR SUPERIOR IMPROVEMENT IN LUNG FUNCTION VS AN ESTABLISHED ICS/LABA[2]

Nearly 2x the lung function improvement vs ADVAIR[2]

LS mean change from baseline in weighted mean FEV_1 (0-24 hours) on Day 84

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Study DB2114930[2]

74 mL Difference (*P*<0.001)
ANORO **165 mL (n=353)**
ADVAIR **91 mL (n=353)**

1.9x IMPROVEMENT

Study DB2114951[2]

101 mL Difference (*P*<0.001)
ANORO **213 mL (n=349)**
ADVAIR **112 mL (n=348)**

The indication for ANORO differs from the indication for ADVAIR in that ANORO is not indicated for reducing COPD exacerbations.

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

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Description of studies[2,3]: The efficacy and safety of a once-daily dose of ANORO ELLIPTA and a twice-daily dose of ADVAIR 250 mcg/50 mcg (administered via the DISKUS inhaler) were evaluated in two 12-week, multicenter, randomized, double-blind, double-dummy, parallel-group studies in patients (mean age range: 63 to 64 years) with COPD with no exacerbations (COPD symptoms requiring oral corticosteroids, antibiotics, and/or hospitalization) in the previous year. At screening, patients had a mean postbronchodilator FEV_1 range of 49.4% to 49.5% predicted. The studies were not powered to compare the safety profiles of the products.

Primary endpoint: Weighted mean FEV_1 (0-24 hours postdose) on Day 84.

COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ICS=inhaled corticosteroid; LAMA=long-acting muscarinic antagonist; LS=least squares.

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- ANORO should not be used more often or at higher doses than recommended or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Caution should be exercised when considering the coadministration of ANORO with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of ANORO. Discontinue ANORO if such reactions occur.

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

Important Safety Information for ANORO ELLIPTA (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO may need to be discontinued. ANORO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO with ketoconazole and other known strong CYP3A4 inhibitors as increased systemic exposure to vilanterol and cardiovascular adverse effects may occur. See prior Warning and Precaution regarding CYP3A4 inhibitors.
- ANORO should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because they may potentiate the effect of vilanterol on the cardiovascular system.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non–potassium-sparing diuretics, as ECG changes and/or hypokalemia associated with these diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

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

References: 1. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. 2019 report. www.goldcopd.org. Accessed November 27, 2018. **2.** Donohue JF, Worsley S, Zu C-Q, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015; 109(7):870-881. **3.** Data on file, GSK.

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

ANORO ELLIPTA was developed in collaboration with INNOVIVA

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

ANORO ELLIPTA **BRIEF SUMMARY**

(umeclidinium and vilanterol inhalation powder), for oral inhalation

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

WARNING: ASTHMA-RELATED DEATH

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

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

1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta$_2$-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death

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

A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 1 5.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.

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

5.2 Deterioration of Disease and Acute Episodes

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

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

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

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

5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting Beta$_2$-agonists

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

5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3) of full prescribing information]*.

5.5 Paradoxical Bronchospasm

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

5.6 Hypersensitivity Reactions

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

5.7 Cardiovascular Effects

Vilanterol, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms *[see Clinical Pharmacology (12.2) of full prescribing information]*. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.8 Coexisting Conditions

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

5.9 Worsening of Narrow-Angle Glaucoma

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

5.10 Worsening of Urinary Retention

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

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

6 ADVERSE REACTIONS

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

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

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials

The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) was 48% (range: 13% to 76%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

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

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

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than placebo included the following: productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

12-Month Trial

In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

6.2 Postmarketing Experience

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

Cardiac Disorders

Palpitations.

Eye Disorders

Blurred vision, glaucoma, increased intraocular pressure.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

Nervous System Disorders

Dysgeusia, tremor.

Psychiatric Disorders

Anxiety.

Renal and Urinary Disorders

Dysuria, urinary retention.

Respiratory, Thoracic, and Mediastinal Disorders

Dysphonia, paradoxical bronchospasm.

(continued on next page)

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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

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

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects

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

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

8.2 Labor and Delivery

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

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

8.3 Nursing Mothers

ANORO ELLIPTA

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

Umeclidinium

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

Vilanterol

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 years and older and 478 subjects aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

10.1 Umeclidinium

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

10.2 Vilanterol

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ANORO ELLIPTA

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

Umeclidinium

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

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

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

Vilanterol

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death

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

Not for Acute Symptoms

Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

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

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

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

Paradoxical Bronchospasm

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

Risks Associated with Beta-agonist Therapy

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

ANORO ELLIPTA was developed in collaboration with INNOVIVA

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised 10/2017 ANR:5BRS

PM-US-UCV-ADVT-180001 December 2018. Produced in USA.

Too much, too little sleep linked to atherosclerosis

BY M. ALEXANDER OTTO
MDedge News

Too little and too much sleep, along with fragmented sleep, were independently linked with increased subclinical, noncardiac atherosclerotic plaque in healthy middle-aged men and women in a Spanish investigation of bank employees.

"Overall, our findings support the potential role of healthy sleeping in protecting against atherosclerosis. Thus, recommending a good sleep hygiene" – 7-8 hours a night – "should be part of the lifestyle modifications provided in our daily clinical practice," said investigators led by Fernando Domínguez, MD, PhD, of Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid. The report is in the Journal of the American College of Cardiology.

Studies have linked sleep problems to increased cardiovascular risk before, but the investigations tended to focus on patients with obstructive sleep apnea (OSA) and other problems, and often relied on patient self-report. The investors wanted to see if the relationship held in healthy adults, using an objective measure.

The participants – all with no known cardiovascular disease – wore Acti Trainers accelerometers (Actigraph, Pensacola, Fla.) around their waists for 7 days to record sleep duration and quality. Subjects also had their plaque burdens assessed by 3-dimensional vascular ultrasound (VUS) at their carotid and femoral arteries bilaterally. Cardiac CT was used to assess coronary artery calcification as a surrogate for coronary artery atherosclerosis.

The 3,974 participants had a mean age of 46 years, and a third were women; they had a low prevalence of both hypertension and diabetes. OSA patients were excluded from the study. Overall, 27% had very short sleep duration (VSSD), less than 6 hours a night; 38% had short sleep duration (SSD), 31% slept from 7 to 8 hours per night, and served as the reference group for healthy sleep habits; and 4% had long sleep duration (LSD), greater than 8 hours.

Wavebreak Media/Thinkstockphotos

After adjustment for a wide range of cardiovascular risk factors, including body mass index, hypertension, and smoking, VSSD was independently associated with a higher atherosclerotic burden, compared to the reference group (odds ratio, 1.27; 95% confidence interval, 1.06-1.52; $P = 0.008$). Participants in the highest quintile of sleep fragmentation were more likely to have plaques at multiple sites (OR, 1.34; 95% CI, 1.09-1.64; $P = 0.006$). The Framingham risk score at both 10 and 30 years was significantly higher in participants with VSSD or SSD, and in the highest quintiles of sleep fragmentation.

LSD was also associated with a higher plaque burden, which reached statistical significance in women. "Too-long sleep duration may not be healthy either ... Recommendations should be restricted to 7 to 8 hours," the investigators said.

Sleep duration and quality were not associated with inflammation markers or coronary artery calcification. The investigators noted that CT for coronary artery calcification might not be as sensitive as VUS for picking up subclinical atherosclerosis.

Short sleepers tended to have higher intakes of alcohol and caffeine than did those in the 7- to 8-hour group.

The work was funded by CNIC and Banco Santander, among others. Dr. Domínguez had no disclosures. Investigator Hector Bueno, MD, PhD, reported research funding and fees from a number of companies, including AstraZeneca and Novartis. The second author, Valentín Fuster, MD, PhD, is the editor of the Journal of the American College of Cardiology, which published the report.

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SOURCE: Domínguez F et al. J Am Coll Cardiol 2019;73:134-44.

Teens' screen time linked to poor sleep, depression

BY JILL D. PIVOVAROV
MDedge News

Screen-based activities and sleep behaviors could be "intervention targets" for adolescents with depressive symptoms, results of a study of almost 3,000 U.S. adolescents suggest.

"Our results indicated that [social messaging, Web surfing, TV/movie watching, and video gaming] were associated with greater depressive symptoms and poorer sleep characteristics," Xian Li, PhD, and her associates reported in Sleep Medicine.

Numerous studies previously have demonstrated a positive link between adolescent depression and exposure to electronic devices, although little is known about the precise mechanism(s) of action involved and to what extent sleep plays a role. To address those gaps, Dr. Li, of the State University of New York at Stony Brook, and her associates examined four types of screen activities to determine whether symptoms of adolescent depression, sleep duration, and symptoms of insomnia – including problems falling asleep and staying asleep – are influenced in any way by those activities.

Using data from the Fragile Families and Child Wellbeing Study, a longitudinal urban birth cohort study, Dr. Li and her associates evaluated a total of 2,865 adolescents (mean 15.53 years of age; 48.2% female). The investigators assessed depressive symptoms at age 15 years by using five items from Center for Epidemiologic Studies Depression Scale.

Dr. Li and her associates found greater depressive symptoms associated with all four of the screen-based activities (P less than .01). In addition, more problems were observed with falling and staying asleep as well as shortened duration of sleep during the week for each of the activities monitored.

Social messaging, Web surfing, and time spent watching TV and movies appeared to be directly correlated with sleep characteristics, but the same could not be said for gaming, which showed only partial correlation with sleep characteristics. In that case, the authors speculated that the association between gaming and depression could be at least partly explained by individual characteristics such as trait neuroticism and self-control or a self-selection behavior in which those exhibiting greater signs of depression turn to gaming as an escape.

The authors also noted a significant link between depressive symptoms at age 9 years and gaming behavior at age 15 years. They did note that, while the relationships in the models might have statistical significance, "the effect size in the study as a whole are small."

The research was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health, and several private foundations. Dr. Buxton received two subcontract grants to Pennsylvania State University from Mobile Sleep Technologies. Dr. Hale received an honorarium from the National Sleep Foundation.

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SOURCE: Li X et al. Sleep Med. 2019 Feb 2. doi: 10.1016/j.sleep.2019.01.029.

Socioeconomic status, race tied to CPAP compliance

BY DOUG BRUNK
MDedge News

SAN DIEGO – Positive indicators of compliance with continuous positive airway pressure (CPAP) included higher apnea-hypopnea index, white race, and higher median household income, results from a large single-center cohort study showed.

"CPAP is the gold standard treatment for OSA [obstructive sleep apnea] and is very effective, especially for those with severe disease," researchers led by Philip S. LoSavio, MD, wrote in an abstract presented at the Triological Society's Combined Sections Meeting. "However, CPAP is a significant challenge for patients for various reasons, with reports of only 46%-80% of OSA patients using CPAP for more than 4 consecutive hours on two out of three nights."

In an effort to identify and define different factors associated with CPAP compliance, Dr. LoSavio and his colleagues collected data on 578 patients with OSA on CPAP who were treated at Rush University Medical Center, Chicago. The mean patient age was 58 years, 52% were female, 43% were African American, 40% were white, their mean body mass index was 36.91 kg/m^2, and their mean apnea-hypopnea index was 37.25 events per hour. The researchers recorded CPAP use at office visits via CPAP module or card, and patients were considered CPAP compliant if their machines logged 4 consecutive hours of use for 70% or more of

Continued on page 29

VIEW ON THE NEWS

Krishna Sundar, MD, FCCP, comments: Striking findings of this study are strong effects of median income and race on CPAP compliance. Other studies have shown improved CPAP compliance following a visit with a sleep provider prior to therapy and in patients with greater self-efficacy. These findings together emphasize the importance of patient characteristics (beyond sleep apnea severity or comorbidities) as determinants of PAP adherence.

More data link short sleep, homocysteine levels, CV risk

BY KARI OAKES
MDedge News

Short sleep's association with cardiovascular risk may be mediated in part by elevated homocysteine levels, suggests a new analysis of data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES).

The study, published in the Journal of Clinical Sleep Medicine, found that elevated homocysteine levels were only associated with short sleep duration for some populations, including women, non-Hispanic white individuals, and participants with obesity.

A total of 4,480 NHANES participants had serum homocysteine levels on record and were included in the study; of these, those with self-reported sleep duration of 7 hours had the lowest serum homocysteine levels. Those with the shortest sleep duration – 5 hours or less per night – had the highest homocysteine levels.

When participants were broken into subgroups by such factors as sex, ethnicity/race, and body mass index, the association between extremely short sleep and elevated homocysteine levels was retained for three groups: women, non-Hispanic white participants, and those with BMIs of 30 kg/m^2 and higher.

"[T]his finding might suggest increased vulnerability to cardiovascular risk or other atherothrombotic events in these groups in the context of short sleep," wrote Tien-Yu Chen, MD, of Tri-Service General Hospital, Taipei, Taiwan, and coauthors in the abstract accompanying the study.

In the NHANES questionnaire, participants were asked how much sleep they usually got, in whole hours. Serum homocysteine was measured once for each study participant.

Using multivariate linear regression, homocysteine was considered the dependent, continuous variable, and the association between sleep duration and homocysteine was assessed using three models that accounted for confounders. The first and simplest model accounted for age, sex, and race/ethnicity. The second model added BMI, several cardiometabolic laboratory values, and vitamin B_6, vitamin B_{12}, and folate levels. The third model included all previous factors and added patient characteristics and comorbidities, such as sleep disorders, mental health service use, cardiovascular disease and cancer diagnoses, and alcohol and tobacco use.

JACKF/THINKSTOCKPHOTOS

Dr. Chen and colleagues dichotomized homocysteine levels to above or below the 75th percentile of the log homocysteine level, which fell at 9.74 nmol/L.

After adjustment, women, but not men, had an association between short sleep and increased odds of elevated homocysteine (odds ratio, 2.691; $P = .010$). This association "persisted in fully adjusted models," wrote Dr. Chen and coauthors.

For individuals with obesity (BMI of 30 or greater), the association between elevated homocysteine and extremely short sleep (5 hours or less) persisted in fully adjusted models (beta = .062; $P = .039$ for model 3).

When looking at ethnicity, the association between extremely short sleep and elevated homocysteine was only seen among non-Hispanic white participants; again, this association was seen after full adjustment for confounders (beta = .068; $P = .032$). Small sample sizes limited some of the racial/ethnic analyses, noted the investigators.

Homocysteine, explained Dr. Chen and coauthors, is associated with a variety of atherogenic changes, and elevated levels are associated with increased risk for cardiovascular disease and mortality. Short sleep is also associated with increased cardiovascular risk, as is long sleep in some studies.

Though preliminary work had shown that short sleep had an association with homocysteine levels, the relationship is unclear since that study had many potential cardiovascular confounders, they said.

The association between extremely short sleep duration and cardiovascular events has been well established, with increased inflammation playing a potential role, although the reasons for the association are still being elucidated. "Because increased homocysteine levels are considered an independent risk factor for cardiovascular diseases, further studies are needed to better understand the relationships among short sleep duration, homocysteine levels, and cardiovascular events," the investigators wrote.

The study's strengths include the large sample size and ability to control for many demographic and individual characteristics, including comorbidities. However, sleep duration was based on self-report and did not include information about napping or sleep-wake times. Also, sleep quality was not assessed beyond a question about snoring or snorting and a question about a prior diagnosis of a sleep disorder.

One of the coauthors reported financial relationships with multiple pharmaceutical companies and UpToDate.

koakes@mdedge.com

SOURCE: Chen T-Y et al. J Clin Sleep Med. 2019;15(1):139-48.

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Indication

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

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The most common side effects of REVATIO greater than or equal to 3% were epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. Adverse events of REVATIO injection were similar to those seen with oral tablets.

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

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

No dose adjustment required for renal impaired.

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

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

PP-REV-USA-0140-02

Printed in USA/May 2018

Revatio® sildenafil 20 mg tablets

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

INDICATION AND USAGE

REVATIO is a phosphodiesterase (PDE-5) indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening.

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

^includes peripheral edema

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

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

Nervous system Seizure, seizure recurrence.

Continued from page 26

nights. During the office visits, patients completed a questionnaire asking if they were suffering from different otolaryngology-related diseases, including sinus headaches, gastroesophageal reflux, and enlarged tonsils. Dr. LoSavio, who heads the section of sleep surgery in the department of otorhinolaryngology at Rush University Medical Center, and his colleagues performed logistic regression to ascertain the effects of race and socioeconomic status on CPAP compliance while adjusting for OSA severity. They also analyzed the adjusted association of median income and self-reported symptoms of sinus headaches, GERD, and enlarged tonsils, on CPAP compliance.

They found that African American patients were less compliant with CPAP, compared with their white counterparts (odds ratio 0.42; *P* less than .01). In addition, patients with mild OSA were less likely to be compliant compared with those who had severe disease (OR 0.57; *P* less than .03). Self-reported symptoms of sinus headaches, GERD, and enlarged tonsils were associated with significantly lower levels of compliance, while higher median income was positively associated with higher levels of compliance. When the researchers grouped incomes based on the 2018 federal tax classification brackets, they observed a significant association between compliance and median income (*P* less than .001), with a likelihood ratio of 20.4.

Self-reported symptoms of sinus headaches, GERD, and enlarged tonsils were associated with significantly lower levels of compliance.

"Previous studies have shown that with increases in OSA disease severity, defined by higher [apnea-hypopnea index], comes increases in CPAP compliance, while other studies have alluded to the fact that lower socioeconomic status can affect CPAP compliance," Dr. LoSavio and his associates wrote in their abstract. "A novel aspect of our study hoped to shed light on different otolaryngology-related diseases and how they might affect compliance. The patients with comorbid GERD, sinus headaches, and enlarged tonsils were less CPAP compliant in our study. These conditions are relatively easily treated and could therefore provide an avenue to increase CPAP compliance if addressed." They acknowledged certain limitations of the study, including its single-center design and the self-reported nature of the patient questionnaire.

David Cannings-Bushell/iStockphoto

The researchers reported having no financial disclosures. The meeting was jointly sponsored by the Triological Society and the American College of Surgeons.

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SOURCE: LoSavio PS et al. Triological CSM 2019, Abstracts.

Sleep problems common in autism spectrum disorder

BY TARA HAELLE
MDedge News

Children with a diagnosis of autism spectrum disorder or another developmental delay or disorder that includes autistic characteristics are twice as likely to have sleeping problems, a multisite case-control study has found.

The findings match up with previous similar studies, but this study is among the largest to measure sleeping problems in children with autism spectrum disorder with two control groups.

"The higher reported occurrence of sleep problems in children with autism spectrum disorder may be due to multiple contributing factors, including physiologic differences, sleep disorders, developmental comorbidities, medical comorbidities causing sleep disruption, communication impairments, and behavioral disturbances," Ann M. Reynolds, MD, of the University of Colorado and Children's Hospital Colorado, both in Aurora, and her associates reported in Pediatrics.

"Children with autism spectrum disorder are more likely to have anxiety, which may predispose them to sleep problems," the authors added.

The study evaluated sleep habits and problems in 1,987 children aged 2-5 years. The study population included 522 children with autism spectrum disorder, 228 children with other developmental delays and disorders that have autism spectrum disorder characteristics, 534 children with other developmental delays and disorders, and 703 children from the general population.

DEYANGEORGIEV/THINKSTOCKPHOTOS

Parents completed the Children Sleep Habits Questionnaire (CSHQ), a 33-item assessment tool typically used with a total score cutoff of 41 and above for identification of children with sleep disorders. The researchers also used a second, more conservative cutoff of 48 – the cutoff for the highest quartile in the general population group to avoid overidentification with the lower cutoff.

Scores were adjusted for maternal education and race/ethnicity, family income, child age and sex, and child cognitive scores on the Mullen Scales of Early Learning (MSEL). The researchers also adjusted for genetic and/or neurologic diagnoses, including Down syndrome, fragile X, Rett syndrome, tuberous sclerosis, cerebral palsy, and neurofibromatosis.

Autistic children tended to have lower MSEL scores than the other children. Both the autistic children and those with other developmental disorders and delays were more likely than those in the general population to have neurologic or genetic conditions.

Based on a cutoff score of 48, autistic children had more than double the odds of sleep problems, compared with children in the general population (adjusted odds ratio, 2.37; $P = .001$) and children with other developmental delays (aOR, 2.12; $P = .001$).

With a cutoff of 41, sleep problems in children with autism spectrum disorder were 1.45 times greater than the general population ($P = .023$) and 1.75 times greater than those with developmental delays ($P = .001$). But children with developmental delays who displayed autistic characteristics did not have significantly different prevalence of sleep problems than children with autism spectrum disorder had.

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: More research in the area of autism is needed. This is a robust study comparing autism to other developmental disorders in ages 2 thru 5 years.

"The phenotypic overlay between children with [autism spectrum disorder]and children with developmental delay with [autism characteristics] may explain the similarities in sleep disturbance among these two groups," the authors wrote.

The research was funded by the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Award. Dr Reynolds consults for Ovid Therapeutics regarding evaluation of sleep severity and improvement in clinical trials.

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SOURCE: Reynolds AM et al. Pediatrics. 2019 Feb. 11. doi: 10.1542/peds.2018-0492.

No increase in severe community-acquired pneumonia after PCV13

BY TARA HAELLE
MDedge News

Despite concern about the rise of nonvaccine serotypes following widespread PCV13 immunization, cases of community-acquired pneumonia (CAP) remain nearly as low as after initial implementation of the vaccine and severe cases have not risen at all.

This was the finding of a prospective time-series analysis study from eight French pediatric emergency departments between June 2009 and May 2017. The 12,587 children with CAP enrolled in the study between June 2009 and May 2017 were all aged 15 years or younger and came from one of eight French pediatric EDs.

Pediatric pneumonia cases per 1,000 ED visits dropped 44% after PCV13 was implemented, a decrease from 6.3 to 3.5 cases of CAP per 1,000 pediatric visits from June 2011 to May 2014, with a slight but statistically significant increase to 3.8 cases of CAP per 1,000 pediatric visits from June 2014 to May 2017. However, there was no statistically significant increase in cases with pleural effusion, hospitalization, or high inflammatory biomarkers.

"These results contrast with the recent increase in frequency of invasive pneumococcal disease observed in several countries during the same period linked to serotype replacement beyond 5 years after PCV13 implementation," reported Naïm Ouldali, MD, of the Association Clinique et Thérapeutique Infantile du Val-de-Marne in France, and associates. The report is in JAMA Pediatrics.

"This difference in the trends suggests different consequences of serotype replacement on pneumococcal CAP vs invasive pneumococcal disease," they wrote. "The recent slight increase in the number of all CAP cases and virus involvement may reflect changes in the epidemiology of other pathogens and/or serotype replacement with less pathogenic serotypes."

This latter point arose from discovering no dominant serotype during the study period. Of the 11 serotypes not covered by PCV13, none appeared in more than four cases.

"The implementation of PCV13 has led to the quasi-disappearance of the more invasive serotypes and increase in others in nasopharyngeal flora, which greatly reduces the frequency of the more severe forms of CAP, but could also play a role in the slight increase in frequency of the more benign forms," the authors reported.

Among the study's limitations was lack of a control group, precluding the ability to attribute findings to any changes in case reporting. And "participating physicians were encouraged to not change their practice, including test use, and no other potential interfering intervention."

Funding sources for this study included the Pediatric Infectious Diseases Group of the French Pediatrics Society, Association Clinique et Thérapeutique Infantile du Val-de-Marne, the Foundation for Medical Research, and a Pfizer Investigator Initiated Research grant.

Dr. Ouldali has received grants from GlaxoSmithKline, and many of the authors have financial ties and/or have received non-financial support from AstraZeneca, Biocodex, GlaxoSmithKline, Merck, Novartis, Pfizer, and/or Sanofi Pasteur.

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SOURCE: Ouldali N et al. JAMA Pediatrics. 2019 Feb 4. doi: 10.1001/jamapediatrics.2018.5273.

THE SPEED THEY WANT WITH THE CONTROL THEY NEED

SPEED

– Better breathing fast—Majority of patients' FEV_1* improvement occurred at 5 minutes in COPD and 15 minutes in asthma[1-5]

– Reduction of rescue use in asthma from Day 1[1,6†]

CONTROL

– Reduction in COPD exacerbations[1]

*1-hour postdose FEV_1 for COPD and 2-hour postdose FEV_1 for asthma.

†In Study 1, SYMBICORT 160/4.5 provided a 70% reduction in albuterol use vs baseline within 1 day of the first dose and a 57% reduction over 12 weeks.

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

Please see study designs on following pages.

- SYMBICORT 160/4.5 for the maintenance treatment of COPD and for reducing COPD exacerbations
- SYMBICORT for asthma patients ≥12 years of age uncontrolled on an ICS

IMPORTANT SAFETY INFORMATION

- Use of long-acting $beta_2$-adrenergic agonists (LABA) as monotherapy (without inhaled corticosteroids [ICS]) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone
- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- SYMBICORT should not be initiated in patients during rapidly deteriorating episodes of asthma or COPD
- Patients who are receiving SYMBICORT should not use additional formoterol or other LABA for any reason
- Localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. Patients should rinse the mouth after inhalation of SYMBICORT
- Lower respiratory tract infections, including pneumonia, have been reported following the administration of ICS
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to ICS. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available ICS
- Caution should be exercised when considering administration of SYMBICORT in patients on long-term ketoconazole and other known potent CYP3A4 inhibitors
- As with other inhaled medications, paradoxical bronchospasm may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of ICS may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- ICS may result in a reduction in growth velocity when administered to pediatric patients

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

The difference is

Symbicort®

(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

THE SPEED THEY WANT...

SYMBICORT 160/4.5 for the maintenance treatment of COPD; SYMBICORT for asthma patients ≥12 years of age uncontrolled on an ICS

BETTER BREATHING—FAST[1-5]

Majority of patients' FEV_1 improvement occurred at 5 minutes in COPD and 15 minutes in asthma[1-5]

COPD: In a serial spirometry subset of patients taking SYMBICORT 160/4.5* (n=121) in the SUN Study, 67% of 1-hour postdose FEV_1 improvement occurred at **5 minutes** on day of randomization and 84% at end of treatment[1-3]

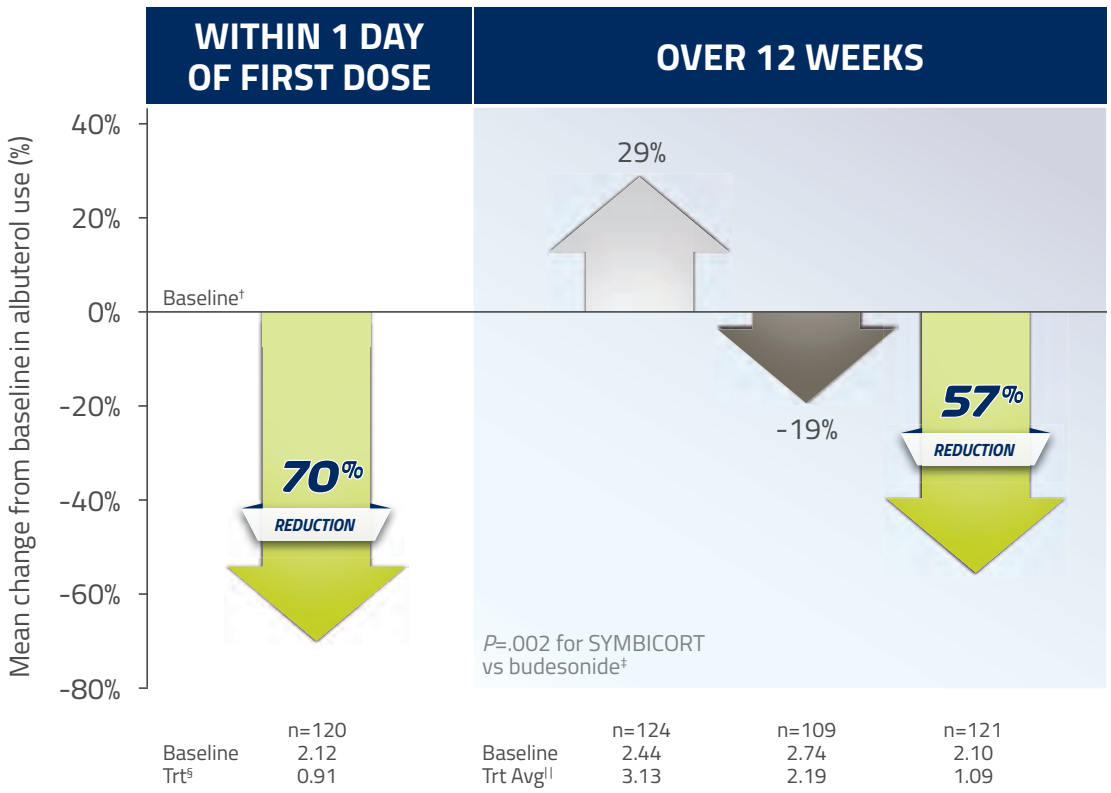
ASTHMA: In patients ≥12 years of age with asthma taking SYMBICORT 160/4.5* (n=124) in Study 1, 79% of 2-hour postdose FEV_1 improvement occurred at **15 minutes** on day of randomization and 90% at end of treatment[1,4,5]

- Sustained improvement in lung function was demonstrated in COPD in a 12-month efficacy and safety study[2,3] and in asthma patients ≥12 years of age in a 12-week efficacy and safety study[4,5]

SYMBICORT for asthma patients uncontrolled on an ICS

REDUCTION OF RESCUE USE FROM DAY 1[1,6]

In Study 1, SYMBICORT 160/4.5 provided a 70% reduction in albuterol use vs baseline within 1 day of the first dose and a 57% reduction over 12 weeks[1,6]



SYMBICORT 160/4.5 mcg*
Budesonide 160 mcg*
Placebo*

Study 1: A 12-week efficacy and safety study of patients ≥12 years of age with moderate to severe asthma[1,6]

- The primary comparison for this secondary endpoint was SYMBICORT vs placebo over 12 weeks ($P<.001$)[1,6‡]

Study 2: A 12-week efficacy and safety study of patients ≥12 years of age with mild to moderate asthma[1,6]

- SYMBICORT 80/4.5 reduced rescue medication use by 51% vs baseline within 1 day of the first dose and 67% over 12 weeks[1,6]

SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms

*Administered as 2 inhalations twice daily. †Baseline is defined as the mean of all values obtained during the run-in period. During run-in, patients received budesonide 80 mcg administered as 2 inhalations twice daily and albuterol as a rescue medication. ‡*P* values based on treatment comparison of absolute mean change from baseline for SYMBICORT vs budesonide and placebo. §Treatment (Trt) is the mean value in puffs/day of albuterol used within 1 day of the first dose of SYMBICORT. ‖Treatment Average (Trt Avg) is defined as the mean of all values obtained during the double-blind treatment period in puffs/day of albuterol.

IMPORTANT SAFETY INFORMATION (cont'd)

- Glaucoma, increased intraocular pressure, and cataracts have been reported following the administration of ICS, including budesonide, a component of SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts
- In rare cases, patients on ICS may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, pharyngitis, rhinitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis
- The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

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

...THE CONTROL THEY NEED

SYMBICORT 160/4.5 for reducing COPD exacerbations

REDUCTION IN COPD EXACERBATIONS

SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations versus formoterol alone[1,7]

Study 4: 12-month exacerbation clinical trial[1,7]

Annual rate estimate: **1.05, formoterol 4.5 mcg* (n=403)**

P<.001 vs formoterol[7]

Estimate rate ratio=0.65;
95% CI: 0.53, 0.80

Annual rate estimate: **0.68, SYMBICORT 160/4.5 mcg* (n=404)**

Study 3: 6-month exacerbation clinical trial. SYMBICORT 160/4.5 significantly reduced the annual rate of moderate/severe COPD exacerbations by 26% vs formoterol (estimate rate ratio=0.74; 95% CI: 0.61, 0.91; *P*=.004)[1,7]

- Annual rate estimate was 0.94 for SYMBICORT 160/4.5 mcg* (n=606) vs 1.27 for formoterol 4.5 mcg* (n=613)

- In **Study 3**, COPD exacerbations were defined as worsening of ≥2 major symptoms (dyspnea, sputum volume, sputum color/purulence) or worsening of any 1 major symptom together with ≥1 of the minor symptoms (sore throat, cold [nasal discharge and/or nasal congestion], fever without other cause, increased cough or increased wheeze) for ≥2 consecutive days. COPD exacerbation severity was classified as moderate if symptoms required systemic corticosteroid (≥3 days) and/or antibiotic treatment, and severe if symptoms required hospitalization
- In **Study 4**, COPD exacerbations were defined as worsening of COPD that required treatment with a course of oral steroids and/or hospitalization

*Administered as 2 inhalations twice daily.

IMPORTANT SAFETY INFORMATION (cont'd)

- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma
- ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT

INDICATIONS

SYMBICORT is indicated for the treatment of asthma in patients 6 years and older not adequately controlled on a long-term asthma-control medication such as an ICS or whose disease warrants initiation of treatment with both an ICS and LABA. (also see DOSAGE AND ADMINISTRATION).

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce COPD exacerbations.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

The difference is

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

COPD

Lung Function Studies

Study 1 (SHINE): A 6-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1704 patients with COPD compared SYMBICORT pressurized metered-dose inhaler (pMDI) 160/4.5 mcg (n=277), SYMBICORT pMDI 80/4.5 mcg (n=281), budesonide 160 mcg (n=275), formoterol 4.5 mcg (n=284), the free combination of budesonide 160 mcg plus formoterol 4.5 mcg (n=287), and placebo (n=300), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 6-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1. The prespecified primary comparison for predose FEV_1 was vs formoterol and for 1-hour postdose was vs budesonide.

Study 2 (SUN): A 12-month, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multicenter study of 1964 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=494), SYMBICORT pMDI 80/4.5 mcg (n=494), formoterol 4.5 mcg (n=495), and placebo (n=481), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD and symptoms for >2 years. The study included a 2-week run-in period followed by a 12-month treatment period. This study was designed to assess change from baseline to the average over the randomized treatment period in predose FEV_1 and in 1-hour postdose FEV_1 (coprimary endpoints). The prespecified primary comparisons for predose FEV_1 were vs placebo and formoterol, and the primary comparison for 1-hour postdose was vs placebo.

COMPARATOR ARMS—Mean improvement in 1-hour postdose FEV_1 (mL/%) over 12 months (serial spirometry subset):

Day of randomization: SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (180 mL/20%), placebo (40 mL/5%).

End of month 12 (last observation carried forward [LOCF]): SYMBICORT 160/4.5 mcg (240 mL/26%), formoterol 4.5 mcg (170 mL/19%), placebo (30 mL/5%).

SYMBICORT 160/4.5 mcg* (n=121)
Formoterol 4.5 mcg* (n=124)
Placebo* (n=125)

Exacerbation Studies

Study 3 (RISE): A 6-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 1219 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=606) with formoterol 4.5 mcg (n=613), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >1 year, and a history of ≥1 moderate or severe COPD exacerbation in the previous year requiring treatment with systemic corticosteroids or hospitalization. The study included a 4-week run-in period, a 26-week randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of moderate and severe COPD exacerbations for SYMBICORT vs formoterol.

Study 4: A 12-month, Phase IIIB, randomized, double-blind, double-dummy, parallel-group, multicenter study of 811 patients with COPD compared SYMBICORT pMDI 160/4.5 mcg (n=407) with formoterol 4.5 mcg (n=404), each administered as 2 inhalations twice daily. Subjects were current or ex-smokers with a smoking history of ≥10 pack-years, aged ≥40 years with a clinical diagnosis of COPD, COPD symptoms for >2 years, and a history of ≥1 COPD exacerbation in the previous year treated with a course of systemic corticosteroids and/or antibiotics. The study included a 2-week run-in period, a 12-month randomized treatment period, and telephone follow-up 2 weeks after end of study completion. This study was designed to assess the annual rate of COPD exacerbations for SYMBICORT vs formoterol.

ASTHMA

Study 1: A 12-week, double-blind, placebo-controlled study comparing SYMBICORT 160/4.5 mcg, budesonide 160 mcg, formoterol 4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, and placebo, each administered as 2 inhalations twice daily. A total of 596 patients (124 randomized to receive SYMBICORT) ≥12 years of age were evaluated. The study included a 2-week run-in period with budesonide 80 mcg, 2 inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of ICS prior to study entry. This study was designed to assess 2 primary endpoints. The first was predose FEV_1 averaged over 12 weeks, and the second was 12-hour average postdose FEV_1 at Week 2. Secondary efficacy variables included daytime and nighttime asthma symptom scores and daily rescue medication use (both recorded by patients in the electronic diary).

COMPARATOR ARMS—Mean change in 2-hour postdose FEV_1 (mL/%) over 12 weeks:

Day of randomization: SYMBICORT 160/4.5 mcg (420 mL/20.0%), budesonide 160 mcg (100 mL/4.4%), formoterol 4.5 mcg (420 mL/19.9%), budesonide 160 mcg + formoterol 4.5 mcg (410 mL/19.4%), placebo (90 mL/4.4%).

End of treatment: SYMBICORT 160/4.5 mcg (420 mL/20.2%), budesonide 160 mcg (140 mL/6.5%), formoterol 4.5 mcg (260 mL/12.3%), budesonide 160 mcg + formoterol 4.5 mcg (410 mL/19.5%), placebo (-10 mL/0.4%).

Mean change from baseline in albuterol use within 1 day of the first dose of study treatment

SYMBICORT 160/4.5 mcg: -70% (n=120)
Budesonide 160 mcg: -14% (n=105)
Formoterol 4.5 mcg: -50% (n=117)
Budesonide 160 mcg + formoterol 4.5 mcg: -70% (n=112)
Placebo: -8% (n=122)

Mean change from baseline in albuterol use over 12 weeks
SYMBICORT 160/4.5 mcg: -57% (n=121)
Budesonide 160 mcg: -19% (n=109)
Formoterol 4.5 mcg: -22% (n=119)
Budesonide 160 mcg + formoterol 4.5 mcg: -67% (n=113)
Placebo: 29% (n=124)

Study 2: A 12-week, randomized, multicenter, double-blind, double-dummy, placebo-controlled study comparing SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, each administered as 2 inhalations twice daily. A total of 480 patients (123 randomized to receive SYMBICORT) ≥12 years of age were evaluated. The study included a 2-week run-in period with placebo and rescue albuterol therapy. Most patients had mild to moderate persistent asthma and were using low to moderate doses of ICS either alone or as part of combination therapy prior to study entry. This study was designed to assess 2 primary endpoints. The first was predose FEV_1 averaged over 12 weeks, and the second was 12-hour average postdose FEV_1 at Week 2. Secondary efficacy variables included daytime and nighttime asthma symptom scores and daily rescue medication use (both recorded by patients in the electronic diary.)

*Administered as 2 inhalations twice daily.

*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.*

References: 1. SYMBICORT [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2017. **2.** Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs.* 2009;69(5):549-565. **3.** Data on file, REF-4960, AZPLP. **4.** Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. *Drugs.* 2006;66:2235-2254. **5.** Data on file, REF-4962, AZPLP. **6.** Data on file, REF-35897, AZPLP. **7.** Data on file, REF-16658, AZPLP.

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

AstraZeneca

The difference is

Symbicort®
(budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

SYMBICORT® (budesonide and formoterol fumarate dihydrate)
Inhalation Aerosol, for oral inhalation use

BRIEF SUMMARY of PRESCRIBING INFORMATION. For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Treatment of Asthma

SYMBICORT is indicated for the treatment of asthma in patients 6 years of age and older.

SYMBICORT should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease

SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. SYMBICORT 160/4.5 is also indicated to reduce exacerbations of COPD. SYMBICORT 160/4.5 is the only strength indicated for the treatment of COPD.

Important Limitations of Use:

- SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

The use of SYMBICORT is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
- Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS

Serious Asthma-Related Events – Hospitalizations, Intubations and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death [see *Salmeterol Multicenter Asthma Research Trial (SMART)*]. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone (see *Serious Asthma-Related Events with ICS/LABA in the full Prescribing Information*).

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared budesonide/formoterol (SYMBICORT) to budesonide *[see Clinical Studies (14.1) in the full Prescribing Information]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N =17,537)[1]	ICS (N =17,552)[1]	ICS/LABA vs ICS Hazard ratio (95% CI)[2]
Serious asthma-related event[3]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta$_2$-adrenergic Agonist
1. Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.
2. Estimated using a Cox proportional hazards model of time to first event with baseline hazards stratified by each of the 3 trials.
3. Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate / salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies

Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

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

As with other inhaled drugs containing beta$_2$adrenergic agents, SYMBICORT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications 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 SYMBICORT should not use an additional LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Local Effects

In clinical studies, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in patients treated with SYMBICORT. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while treatment with SYMBICORT continues, but at times therapy with SYMBICORT 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.

Pneumonia and Other Lower Respiratory Tract Infections

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

In a 6-month lung function study of 1704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g., bronchitis, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In a 12-month lung function study of 1964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6-month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox 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 affects 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 exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If 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 chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension.

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or noncorticosteroid asthma therapy (n=92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%), compared to patients treated with noncorticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

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

Transferring Patients From Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. 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 per day 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 SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe asthma attack 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, a severe asthma attack, or a severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma or 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 inhaled corticosteroids or SYMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercorticism and Adrenal Suppression

Budesonide, a component of SYMBICORT, will often help control asthma and COPD symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT 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, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information].*

Paradoxical Bronchospasm and Upper Airway Symptoms

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

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm.

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia *[see Overdosage (10) in the full Prescribing Information].* Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

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

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month lung function study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm^2). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, BMD for total hip and total spine regions for the 12-month time point were stable over the entire treatment period.

Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled

corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4) in the full Prescribing Information]*.

Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore, close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5 mcg, or placebo on development of cataracts or glaucoma were evaluated in a subset of 461 patients with COPD in the 12-month lung function study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 160/4.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

SYMBICORT, 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$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia and Hyperglycemia

Beta-adrenergic 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. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, death *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.12) in the full Prescribing Information]*.

Systemic and inhaled corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Pneumonia or lower respiratory tract infections in patients with COPD *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Immunosuppression *[see Warnings and Precautions (5.6) in the full Prescribing Information]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8) in the full Prescribing Information]*
- Growth effects in pediatric patients *[see Warnings and Precautions (5.14) in the full Prescribing Information]*
- Glaucoma and cataracts *[see Warnings and Precautions (5.15) in the full Prescribing Information]*

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.

Clinical Trials Experience in Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT 80/4.5 or 160/4.5 taken 2 inhalations once or twice daily for 12 to 52 weeks. In these trials, the patients on SYMBICORT had a mean age of 38 years and were predominantly Caucasian (82%).

The incidence of common adverse events in Table 2 below is based upon pooled data from three 12-week, double-blind, placebo-controlled clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV_1 at baseline of 76 and 68 for the 80/4.5 mcg and 160/4.5 mcg treatment groups, respectively. Control arms for comparison included 2 inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily dosing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 2 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients 12 years and older

Treatment[1]	SYMBICORT		Budesonide		Formoterol	Placebo
Adverse Event	**80/4.5 N = 277 %**	**160/4.5 N = 124 %**	**80 mcg N = 121 %**	**160 mcg N = 109 %**	**4.5 mcg N = 237 %**	**N = 400 %**
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral Candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	**77.7**	**73.8**	**77.0**	**71.4**	**62.4**	**55.9**

1. All treatments were administered as 2 inhalations twice daily.

Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis assessments.

Pediatric Patients 6 to Less than 12 Years of Age

The safety data for pediatric patients aged 6 to less than 12 years is based on 1 trial of 12 weeks treatment duration. Patients (79 female and 105 male) receiving inhaled corticosteroid at trial entry were randomized to SYMBICORT 80/4.5 (n=92) or budesonide pMDI 80 mcg (n=92), 2 inhalations twice daily. The overall safety profile of these patients was similar to that observed in patients 12 years of age and older who received SYMBICORT 80/4.5 twice daily in studies of similar design. Common adverse reactions that occurred in patients treated with SYMBICORT 80/4.5 with a frequency of ≥3% and more frequently than patients treated only with budesonide pMDI 80 mcg included upper respiratory tract infection, pharyngitis, headache, and rhinitis.

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below reflect exposure to SYMBICORT 160/4.5 in 1783 patients. SYMBICORT 160/4.5 was studied in two placebo-controlled lung function studies (6 and 12 months in duration), and two active-controlled exacerbation studies (6 and 12 months in duration) in patients with COPD.

The incidence of common adverse events in Table 3 below is based upon pooled data from two double-blind, placebo-controlled lung function clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93%) patients with a mean age of 63 years, and a mean percent predicted FEV_1 at baseline of 33%. Control arms for comparison included 2 inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 3 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Table 3 Adverse reactions occurring at an incidence of ≥ 3% and more commonly than placebo in the SYMBICORT group: pooled data from two double-blind, placebo-controlled clinical COPD trials

Treatment[1]	SYMBICORT	Budesonide	Formoterol	Placebo
Adverse Event	**160/4.5 N = 771 %**	**160 mcg N = 275 %**	**4.5 mcg N = 779 %**	**N = 781 %**
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract infection viral	3.5	1.8	3.6	2.7
Average Duration of Exposure (days)	**255.2**	**157.1**	**240.3**	**223.7**

1. All treatments were administered as 2 inhalations twice daily.

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, hematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

The safety findings from the two double-blind, active-controlled exacerbations studies (6 and 12 months in duration) in which 1012 adult COPD patients (616 males and 396 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily were consistent with the lung function studies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMBICORT. 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. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.
Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles, palpitations
Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients
Eye disorders: cataract, glaucoma, increased intraocular pressure
Gastrointestinal disorders: oropharyngeal candidiasis, nausea
Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema, bronchospasm, urticaria, exanthema, dermatitis, pruritus
Metabolic and nutrition disorders: hyperglycemia, hypokalemia
Musculoskeletal, connective tissue, and bone disorders: muscle cramps
Nervous system disorders: tremor, dizziness
Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness
Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation
Skin and subcutaneous tissue disorders: skin bruising
Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Inhibitors of Cytochrome P4503A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.9) in the full Prescribing Information]*.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of COPD and asthma patients received tricyclic antidepressants, and, therefore, no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

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-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 SYMBICORT with non-potassium-sparing diuretics.

OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, single doses of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in adolescent and adult asthma patients 12 years of age and older, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reactions observed in any of these studies.

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur *[see Warnings and Precautions (5) in the full Prescribing Information]*. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

Formoterol

An overdose of formoterol 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. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days.

Treatment of formoterol overdosage consists of discontinuation of the medication 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. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France Rev. 12/2017 US-17406 1/18

Mild OSA resolves spontaneously in some children

BY DOUG BRUNK
MDedge News

CORONADO, CALIF. – Mild obstructive sleep apnea (OSA) resolves in about one-third of children younger than age 3 years after an observation period of 3-12 months, results from a single-center study showed.

"OSA affects up to 6% of the pediatric population, and diagnosis of young children can be particularly challenging due to the heterogeneity of presenting symptoms," Douglas C. von Allmen, MD, said at the Triological Society's Combined Sections Meeting. "While school-age children may present with snoring, that's less common in the younger population. Up to one-quarter of infants may have noisy breathing, which may mimic obstructive events throughout the first 3 years of life. Additionally, long-term clinical implications of mild sleep apnea in very young children is unclear."

According to Dr. von Allmen, a fifth-year otolaryngology resident at the University of Cincinnati, management strategies of children with OSA can include a period of observation, particularly when there's an absence of concerning findings on polysomnography (PSG), such as hypoventilation or significant hypoxia, or when the primary etiology of the OSA is unknown. "Additionally, few studies at this point have attempted to characterize the natural history of mild OSA in pediatric patients under 3 years of age," he said.


Dr. von Allmen

In an effort to assess the effects of observation on the PSG outcomes of children under 3 years with mild OSA, Dr. von Allmen and his colleagues performed a retrospective review of 26 children who had an overnight PSG with a follow-up PSG performed 3-12 months later. They excluded patients with neuromuscular disease, tracheostomy, or interstitial lung disease. All PSGs were performed at the Cincinnati Children's Hospital Medical Center between 2012 and 2017 and were scored by a board-certified sleep physician. The researchers defined mild OSA as at least one, but fewer than five, events per hour. The mean age of the 26 patients was 7 months, 65% were male, 92% were white, and their median body mass index was in the 39th percentile. Comorbidities include laryngomalacia (40%), cardiac disease (40%), allergies (34%), asthma (23%), and Down syndrome (11%).

Between baseline and follow-up, the apnea-hypopnea index (AHI) trended downward from 4.3 to 3.4 events per hour ($P = .19$) the obstructive AHI decreased significantly from 2.7 to 1.3 events per hour ($P = .013$), while the central apnea index also trended downward from 1.4 to 1.2 events per hour ($P = .60$). The oxyhemoglobin nadir and sleep efficiency did not change significantly, but there was a decrease in the arousal index (from 14.7 to 13 events per hour; $P = .027$) and in the percentage of REM sleep (from 33% to 30%; $P = .008$).

As for postobservation OSA severity outcomes, eight patients (31%) resolved spontaneously, one patient progressed from mild to moderate OSA, and the rest remained in their mild OSA state. Subanalysis revealed that OSA resolution rate was 36% in patients with laryngomalacia, compared with 27% in those with no laryngomalacia, a difference that did not reach statistical significance ($P = .98$).

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: While retrospective, this study is important because surgery in children, especially 2 years of age and younger, has a higher incidence of complications.

Dr. von Allmen pointed out that the study cohort had comorbidities which may have contributed to the persistence of OSA. He also acknowledged certain limitations of the study, including its retrospective nature, the potential for selection bias, the small sample size, and the fact that it did not include a control sample of normal children.

Dr. von Allmen reported having no financial disclosures. The study received a resident research award at the meeting, which was jointly sponsored by the Triological Society and the American College of Surgeons.

dbrunk@mdedge.com

SOURCE: von Allmen DC et al. Triological CSM, Abstracts.

FDA approves 0.5-mL Fluzone Quadrivalent vaccine for children

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has approved the 0.5-mL dosage of Fluzone Quadrivalent, an influenza vaccine, for use in children aged 6-35 months, according to Sanofi Pasteur, the vaccine's manufacturer.

FDA approval was based on results of a phase 4 safety and immunogenicity study of nearly 2,000 children. Children aged 6-35 months who received one or two doses of Fluzone at 0.50 mL had a safety profile similar to that of children who received one or two doses of Fluzone at 0.25 mL. Results from the study were presented at the Pediatric Academic Societies annual meeting in April 2018.

This flu vaccine should not be given to anyone with a severe allergic reaction (anaphylaxis) to egg or egg products, according to the press release.

In children, the most common adverse events are injection-site reactions, muscle aches, fatigue, and headache; in young children, irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever are common.

"Offering pediatricians the convenience of the same 0.5-mL dose option for children may help streamline immunization efforts. The potentially life-threatening effects of influenza in children reported during the 2017-18 season, especially among those who were not vaccinated, is sobering," David P. Greenberg, MD, regional medical head of Sanofi Pasteur of North America, said in the press release.

Find the full press release on the Sanofi website.

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CHEST Foundation's NetWorks Challenge is just around the corner

The NetWorks Challenge is an annual fundraising competition that encourages NetWork members to contribute to the CHEST Foundation - supporting clinical research grants and community service programs and creating patient education materials - while earning travel grants for their NetWork members to the CHEST Annual Meeting 2019 in New Orleans. Because of your generosity throughout the 2018 NetWorks Challenge, the CHEST Foundation was able to send 59 early career clinicians to CHEST 2018 in San Antonio - marked growth from the 25 clinicians who received the travel grants in 2017.

As we further improve this program based on feedback from NetWorks members, a few elements of the fundraiser are changing in 2019.

Length: This year, the NetWorks Challenge will span 3 months. Contributions made between April 1 and June 30 count toward your NetWork's fundraising total! Just be sure to list your NetWork when making your contribution on chestfoundation.org/donate. Each month has a unique theme related to CHEST, so be sure to watch our social media profiles to engage with us and each other during the drive.

Additionally, ANY contributions made to the CHEST Foundation during your membership renewal will count toward your NetWorks total amount raised - no matter when your membership is up for renewal. Contributions made in this manner after June 30 will count toward your Network's 2020 amount raised.

Prizes: This year, every NetWork is eligible to receive travel grants to CHEST 2019 in New Orleans based on the amount raised by the NetWork. Our final winners – the NetWork with the highest amount raised, and the NetWork with the highest percentage of participation from their NetWork, will each receive two additional travel grants to CHEST 2019. Plus, the NetWork with the highest amount raised over the course of the challenge receives an additional prize – a seat in a CHEST Live Learning course of the winner's choosing, offered at CHEST's Innovation, Simulation, and Training Center in Glenview, Illinois.

Visit chestfoundation.org/nc for more detailed information.

PRACTICE MANAGEMENT

EHR stress predicts burnout

BY GREGORY TWACHTMAN
MDedge News

Physicians who experience stress related to the use of health information technology are twice as likely to experience burnout.

Rebekah Gardner, MD, of Brown University in Providence, R.I., and her colleagues surveyed all 4,197 Rhode Island physicians in 2017 to learn how the use of electronic health records affected their practices and their job satisfaction.

Just over a quarter (25.0%) of 1,792 respondents reported burnout. Among electronic health record users (91% of respondents), 70% reported health IT–related stress (J Am Med Inform Assoc. 2019;26[2]:106-14; doi: 10.1093/jamia/ocy145).

"After adjustment, physicians reporting poor/marginal time for documentation had 2.8 times the odds of burnout (95% confidence interval, 2.0-4.1; *P* less than .0001) compared to those reporting sufficient time," according to the researchers.

LEAH-ANNE THOMPSON/THINKSTOCK

The team looked at three stress-related variables: whether the EHR adds to the frustration of one's day; whether physicians felt they had sufficient time for documentation; and the amount of time spent on the EHR at home. Variables were measured on a four- or five-point scale depending on the question related to the specific stress variable.

Almost two-thirds (64.2%) of respondents "agreed" or "strongly agreed" that EHRs add to the frustration of their day.

"It was the most commonly cited HIT-related stress measure in almost every specialty, with the highest prevalence among emergency physicians (77.6%)," the investigators wrote.

More than a third of physicians (37.7%) reported "moderately high" or "excessive" time spent on EHRs at home; this metric was the most commonly cited stress measure among pediatricians (63.6%).

Nearly half (46.4%) of physicians reported "poor" or "marginal" sufficiency of time for documentation.

"Presence of any 1 of the HIT-related stress measures was associated with approximately twice the odds of burnout among physician respondents," Dr. Gardner and her colleagues noted, adding that "measuring and addressing HIT-related stress is an important step in reducing workforce burden and improving the care of our patients."

To alleviate burnout, the authors recommended increased use of scribes, use of medical assistants to help create a more team-based documentation function, improved EHR training, more time during the day for documentation, and streamlined documentation expectations, with certain culture shifts needed in some cases (i.e., banning work-related email and clinical tasks for vacationing physicians).

gtwachtman@mdedge.com

SOURCE: Gardner R et al. J Am Med Inform Assoc. doi: 10.1093/jamia/ocy145.

VIEW ON THE NEWS

Mike Nelson, MD, FCCP, comments: I just dictated a note into my EHR about a patient with Buerger disease, thromboangiitis obliterans, translated by my software as thrombo in GI disability her aunts (yes, it is medical software). After laughing, I deleted and tried again only to get the same result. Had I typed this at my electrifying speed of 25 words a minute with eight mistakes it probably would have taken less time by half. Had I written it on a piece of paper it may have taken about 2-3 seconds. Just a few seconds, you say. But multiply it by hundreds of times per day and one can understand the frustration of the 70% in this article. Don't get me started on the 8-page office notes from a problem-focused return visit. Many of you are probably aware that there is an Office of the National Coordinator for Health Information Technology (ONC) that was created in 2004 by an executive order and legislatively mandated in 2009 by the HITECH act. The mission of the organization is to "Improve the health and well-being of individuals and communities through the use of technology and health information that is accessible when and where it matters most." Fifteen years later the ONC is desperately failing in their mission.

Get ready for the Big Easy

CHEST 2019 will be in New Orleans, Louisiana, this year, October 19-23. Here are a few ways to be engaged leading up to the meeting.

Submit abstracts and case reports

Do you have original investigative research to share? There's still some time to submit your abstracts and case reports for presentation at CHEST 2019 through Friday, March 15. If accepted, all abstracts and case reports will be published as submitted in an online *CHEST*® journal abstract supplement. No corrections will be made once submission is complete.

View submission details (https://chestmeeting.chestnet.org/abstracts-and-case-reports/).

Call for moderators

CHEST is currently requesting moderators to facilitate discussions, questions, and answers within assigned sessions on-site at CHEST 2019 in New Orleans. Moderators will be notified June to September of their acceptance as a moderator.

View complete details (https://docs.google.com/forms/d/e/1FAIpQLSd-SWFSyKAeIjfyYgGRF6km_95zn-ba63bx6iM9TWl08gpdqzEQ/viewform).

CHEST Challenge 2019

US-based CHEST fellows-in-training - does your fellowship have what it takes to win CHEST Challenge 2019? CHEST Challenge is a fun and exciting competition in which CHEST fellows-in-training compete against programs around the country for honor and prizes! The first round of the competition consists of two parts: social media challenges and online quiz. The aggregate score for both of these components will be used to identify the top three highest scoring teams. These top three teams will then be invited to send three fellows each to the CHEST Challenge Championship, a Jeopardy-style game show that takes place live during the CHEST Annual Meeting.

See the rules and how to participate (chestchallenge.org).

Apply for CHEST Foundation grants

The CHEST Foundation has awarded more than $10 million in grant funding to nearly 800 recipients worldwide for clinical research and community service. Each year, the CHEST Foundation offers grants to worthy research candidates, generous community service volunteers, and distinguished scholars in a field of expertise.

The CHEST Foundation has awarded more than $10 million in grant funding to nearly 800 recipients worldwide for clinical research and community service.

The CHEST Foundation is accepting grant applications now through April 8, 2019, in the following areas:

- CHEST Foundation Community Service Grant Honoring D. Robert McCaffree, MD, Master FCCP – Up to $15,000 (multiple recipients selected)*
- The GlaxoSmithKline Distinguished Scholar in Respiratory Health – $150,000*
- CHEST Foundation Research Grant in Asthma – $15,000 – $30,000*
- CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease – $25,000 – $50,000*
- CHEST Foundation Research Grant in Cystic Fibrosis – $15,000 – $30,000*
- CHEST Foundation Research Grant in Lung Cancer – $50,000 – $100,000*
- CHEST Foundation Research Grant in Nontuberculous Mycobacteria Diseases – $30,000 – $60,000*
- CHEST Foundation Research Grant in Pulmonary Arterial Hypertension – $25,000 – $50,000*
- CHEST Foundation Research Grant in Pulmonary Fibrosis – $25,000 – $50,000*
- CHEST Foundation Research Grant in Venous Thromboembolism – $15,000 – $30,000*
- CHEST Foundation Research Grant in Women's Lung Health – $10,000*

*Amount contingent on funding.

Learn more on how to apply now. (https://foundation.chestnet.org/grants/apply-for-a-grant/)

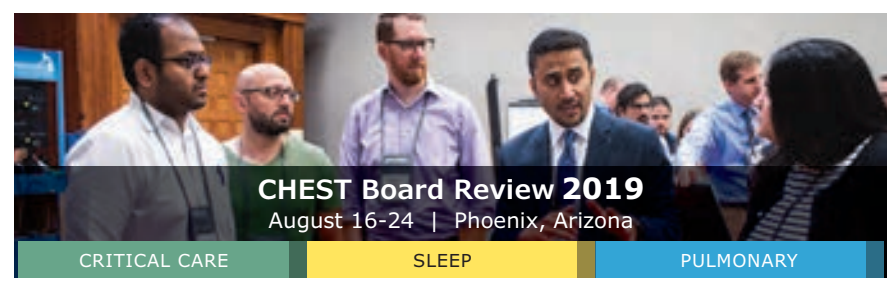
2019 Education Calendar

CHEST Innovation, Simulation, and Training Center in Glenview, Illinois

Learn More **livelearning.chestnet.org**

March 7 - 9	**Ultrasonography: Essentials in Critical Care**
March 21-23	**Lung Cancer: A Multidisciplinary Update**
April 4 - 6	**Critical Skills for Critical Care: A State-of-the-Art Update and Procedures for ICU Providers**
May 3 - 4	**Bronchoscopy Procedures for the ICU**
May 30 - June 1	**Advanced Critical Care Echocardiography**
June 6 - 8	**Difficult Airway Management**
June 28 - 29	**Therapeutic Bronchoscopy for Airway Obstruction**
July 25 - 27	**Mechanical Ventilation: Advanced Critical Care Management**
August 8 - 10	**Cardiopulmonary Exercise Testing (CPET)**
September 5 - 7	**Difficult Airway Management**
September 12 - 14	**Ultrasonography: Essentials in Critical Care**
September 19 - 21	**Comprehensive Bronchoscopy With Endobronchial Ultrasound**
November 7-9	**Extracorporeal Support for Respiratory and Cardiac Failure in Adults**
November 14 - 16	**Critical Care Ultrasound: Integration into Clinical Practice**
November 22 - 23	**Comprehensive Pleural Procedures**
December 5 - 7	**Ultrasonography: Essentials in Critical Care**
December 13 - 14	**Advanced Critical Care Echocardiography Board Review Exam Course**

CHEST®



Calendar subject to change. For most current course list and more information, visit livelearning.chestnet.org.

CHEST reaccredited by Society for Simulation in Healthcare

The American College of Chest Physicians (CHEST) received reaccreditation from the Society for Simulation in Healthcare (SSH) for the 2018-2023 term in the areas of Teaching/Education, Assessment, and Research.

In 2013, CHEST became the first and only medical specialty society to achieve SSH accreditation, a distinction that continues today. Currently, CHEST joins over 125 SSH-accredited programs worldwide, including universities, hospitals, and medical education companies.

The reaccreditation process was the result of months of preparation on behalf of CHEST Simulation Program staff, CHEST Accreditation staff, CHEST Outcomes staff, as well as CHEST's Live Learning Domain Task Force chairs and other education leadership. This culminated in mid-November at a face-to-face on-site interview with site reviewers representing SSH and CHEST Simulation Program faculty and staff and CHEST leadership.

Throughout the process, CHEST was given the opportunity to highlight the unique and innovative ways in which we are utilizing simulation-based education to provide greater clinical insights to enhance patient care.

We recognize that this isn't only an every-4-year commitment, but it is resultant of the ongoing efforts from a group of dedicated individuals.

Thank you to all whose contributions ensured our success!

This month in the journal *CHEST*®

Editor's picks

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

Giants in Chest Medicine – Paul D. Stein, MD, Master FCCP

Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials.
By Dr. E. J. Schenck, et al.

The Accuracy of Clinical Staging of Stage I-IIIa Non-Small Cell Lung Cancer: An Analysis Based on Individual Participant Data.
By Dr. N. Navani, et al.

A Simple Clinical Risk Score (C2HEST) for Predicting Incident Atrial Fibrillation in Asian Subjects.
By Dr. Y-G Li, et al.

A Sleep Medicine Curriculum for Pulmonary and Pulmonary/Critical Care Fellowship Programs: A Multisociety Expert Panel Report.
By Dr. D. A. Schulman, et al.

Therapy for Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report.
By J. R. Klinger, et al.

SLEEP STRATEGIES

Phrenic nerve stimulation for treatment of central sleep apnea

BY SHAHROKH JAVAHERI, MD, FCCP; ROBIN GERMANY, MD; WILLIAM T. ABRAHAM, MD; AND MARIA ROSA COSTANZO, MD

Compared with obstructive sleep apnea (OSA), the prevalence of central sleep apnea (CSA) is low in the general population. However, in adults, CSA may be highly prevalent in certain conditions, most commonly among those with left ventricular systolic dysfunction, left ventricular diastolic dysfunction, atrial fibrillation, stroke, and opioid users (Javaheri S, et al. *J Am Coll Cardiol.* 2017; 69:841). CSA may also be found in patients with carotid artery stenosis, cervical neck injury, and renal dysfunction. CSA can occur when OSA is treated (treatment-emergent central sleep apnea, or TECA), notably, and most frequently, with continuous positive airway pressure (CPAP) devices. Though in many individuals, this frequently resolves with continued use of the device.

Dr. Javaheri

In addition, unlike OSA, adequate treatment of CSA has proven difficult. Specifically, the response to CPAP, oxygen, theophylline, acetazolamide, and adaptive-servo ventilation (ASV) is highly variable, with individuals who respond well, and individuals in whom therapy fails to fully suppress the disorder.

Our interest in phrenic nerve stimulation increased after it was shown that CPAP therapy failed to improve morbidity and mortality of CSA in patients with heart failure and reduced ejection fraction (HFrEF) (CANPAP trial, Bradley et al. *N Engl J Med.* 2005;353[19]:2025). In fact, in this trial, treatment with CPAP was associated with significantly increased mortality during the first few months of therapy. We reason that a potential mechanism was positive airway pressure that had adverse cardiovascular effects (Javaheri S. *J Clin Sleep Med.* 2006;2:399). This is because positive airway pressure therapy decreases venous return to the right side of the heart and increases lung volume. This could increase pulmonary vascular resistance (right ventricular afterload), which is lung volume-dependent. Therefore, the subgroup of individuals with heart failure whose right ventricular function is preload-dependent and has pulmonary hypertension is at risk for premature mortality with any PAP device.

Interestingly, investigators of the SERVE-HF trial (Cowie MR, et al. *N Engl J Med*. 2015;373:1095) also hypothesized that one reason for excess mortality associated with ASV use might have been due to an ASV-associated excessive rise in intrathoracic pressure, similar to the hypothesis we proposed earlier for CPAP. We expanded on this hypothesis and reasoned that based on the algorithm of the device, in some patients, it could have generated excessive minute ventilation and pressure contributing to excess mortality, either at night or daytime (Javaheri S, et al. *Chest*. 2016;149:900). Other deficiencies of the algorithm of the ASV device could have contributed to excess mortality as well (Javaheri S, et al. *Chest*. 2014;146:514). These deficiencies of the ASV device used in the SERVE-HF trial have been significantly improved in the new generation of ASV devices.

Undoubtedly, therefore, mask therapy with positive airway pressures increases intrathoracic pressure and will adversely affect cardiovascular function in some patients with heart failure. Another issue for mask therapy is adherence to the device remains poor, as demonstrated both in the CANPAP and SERVE-HF trials, confirming the need for new approaches utilizing non-mask therapies both for CSA and OSA.

Given the limitations of mask-based therapies, over the last several years, we have performed studies exploring the use of oxygen, acetazolamide, theophylline, and, most recently, phrenic nerve stimulation (PNS). In general, these therapies are devoid of increasing intrathoracic pressure and are expected to be less reliant on patients' adherence than PAP therapy. Long-term randomized clinical trials are needed, and, most recently, the NIH approved a phase 3 trial for a randomized placebo-controlled low flow oxygen therapy for treatment of CSA in HFrEF. This is a modified trial proposed by one of us more than 20 years ago!

Regarding PNS, CSA is characterized by intermittent phrenic nerve (and intercostal nerves) deactivation. It, therefore, makes sense to have an implanted stimulator for the phrenic nerve to prevent development of central apneas during sleep. This is not a new idea. In 1948, Sarnoff and colleagues demonstrated for the first time that artificial respiration could be effectively administered to the cat, dog, monkey, and rabbit in the absence of spontaneous respiration by electrical stimulation of one (or both) phrenic nerves (Sarnoff SJ, et al. *Science.* 1948;108:482). In later experiments, these investigators showed that unilateral phrenic nerve stimulation is also equally effective in man as that shown in animal models.

The phrenic nerves come in contact with veins on both the right (brachiocephalic) and the left (pericardiophrenic vein) side of the mediastinum. Like a cardiac pacemaker, an electrophysiologist places the stimulator within the vein at the point of encounter with the phrenic nerve. Only unilateral stimulation is needed for the therapy. The device is typically placed on the right side of the chest as many patients may already have a cardiac implanted electronic device such as a pacemaker. Like the hypoglossal nerve stimulation, the FDA approved this device for the treatment of OSA. The system can be programmed using an external programmer in the office.

Phrenic nerve stimulation system is initially activated 1 month after the device is placed. It is programmed to be automatically activated at night when the patient is at rest. First, a time is set on the device for when the patient typically goes to bed and awakens. This allows the therapy to activate. The device contains a position sensor and accelerometer, which determine position and activity level. Once appropriate time, position, and activity are confirmed, the device activates automatically. Therapy comes on and can increase in level over several minutes. The device senses transthoracic impedance and can use this measurement to make changes in the therapy output and activity. If the patient gets up at night, the device automatically stops and restarts when the patient is back in a sleeping position. How quickly the therapy restarts and at what energy is programmable. The device may allow from 1 to 15 minutes for the patient to get back to sleep before beginning therapy. These programming changes allow for patient acceptance and comfort with the therapy, even in very sensitive patients. Importantly, no patient activation is needed, so therapy delivery is independent of patient's adherence over time.

In the prospective, randomized pivotal trial (Costanzo et al. Lancet. 2016;388:974), 151 eligible patients with moderate-severe central sleep apnea were implanted and randomly assigned to the treatment (n=73) or control (n=78) groups. Participants in the active arm received PNS for 6 months. All polysomnograms were centrally and blindly scored. There were significant decreases in AHI (50 to 26/per hour of sleep), CAI (32 to 6), arousal index (46 to 25), and ODI (44 to 25). Two points should be emphasized: first, changes in AHI with PNS are similar to those in CANPAP trial, and there remained a significant number of hypopneas (some of these hypopneas are at least in part related to the speed of the titration when the subject sits up and the device automatically is deactivated, only to resume therapy in supine position); second, in contrast to the CANPAP trial, there was a significant reduction in arousals. Probably for this reason, subjective daytime sleepiness, as measured by the ESS, improved. In addition, PNS improved quality

Continued on page 46

In memoriam

CHEST has been notified of the following deaths.
We extend our sincere condolences.

Faroque A. Khan, MBBS
Venessa Holland, MD, FCCP

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

#1 prescribed biologic indicated for severe eosinophilic asthma*— 27,000 patients and counting[1†]

*Source: IQVIA - NPA™ audit: 12 mo. TRX data ending 7/18 (All rights reserved).

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Opportunistic Infections: Herpes Zoster

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

Reduction of Corticosteroid Dosage

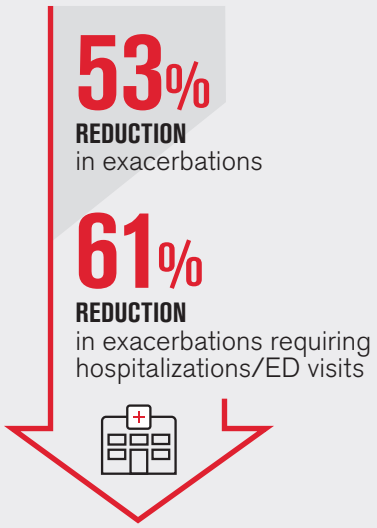
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decreases in corticosteroid doses, if appropriate, should be gradual and under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms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

Parasitic (Helminth) Infection

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

Choose NUCALA:

Powerful Protection From Exacerbations[2‡]



Powerful Reduction in OCS Dose[3]

Lasting Evidence[1]

Only anti-interleukin 5 (IL-5) with a

4.5-year

open-label study that evaluated safety and efficacy

MENSA (Trial 2)[2]: 32-week study comparing NUCALA 100 mg to placebo, each added to SOC in 576 patients with severe eosinophilic asthma (SEA). **Primary Endpoint Results:** Frequency of exacerbations. NUCALA: 0.83/year, placebo: 1.74/year; *P*<0.001). **Secondary Endpoint Results:** Frequency of exacerbations requiring hospitalization and/or ED visit; NUCALA: 0.08/year; placebo: 0.20/year; *P*=0.02.

SIRIUS (Trial 3)[3]: 24-week study comparing NUCALA 100 mg to placebo in 135 patients with SEA receiving prednisone 5-35 mg (or equivalent) per day and regular use of high-dose ICS and 1 other controller. **Primary Endpoint Results:** Percent reduction in daily OCS dose (Weeks 20 to 24) while maintaining asthma control vs placebo; *P*=0.008.

COLUMBA[1]: 4.5-year open-label study assessing the safety, immunogenicity, and efficacy of NUCALA 100 mg added to asthma controller therapy in 347 patients with SEA.

‡ Worsening of asthma that required use of oral/systemic corticosteroids and/or hospitalizations and/or emergency department (ED) visits; for patients on maintenance oral/systemic corticosteriods, exacerbations were defined as requiring at least double the existing maintenance dose for at least 3 days.

Standard of care (SOC)=regular treatment with high-dose inhaled corticosteroids (ICS) and at least 1 other controller with or without oral corticosteroids (OCS).

Learn more at **KnowNucalaHCP.com**

IMPORTANT SAFETY INFORMATION (cont'd)

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.

USE IN SPECIFIC POPULATIONS

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

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

References: 1. Data on file, GSK. **2.** Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371:1198-1207. **3.** Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371:1189-1197.

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

Printed in USA. 1007315R0 September 2018

Nucala
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

BRIEF SUMMARY

NUCALA
(mepolizumab) for injection, for subcutaneous use

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

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Acute Asthma Symptoms or Deteriorating Disease

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

5.3 Opportunistic Infections: Herpes Zoster

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

5.4 Reduction of Corticosteroid Dosage

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

5.5 Parasitic (Helminth) Infection

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience in Severe Asthma

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

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

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

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

52-Week Trial

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

Systemic Reactions, including Hypersensitivity Reactions

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

Injection Site Reactions

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

Long-term Safety

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

6.3 Immunogenicity

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

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

6.4 Postmarketing Experience

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

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

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

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8 USE IN SPECIFIC POPULATIONS (cont'd)

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

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

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

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

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

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

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

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

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

Manufactured by
GlaxoSmithKline LLC
Philadelphia, PA 19112
U.S. License Number 1727

Distributed by

GlaxoSmithKline
Research Triangle Park, NC 27709

Printed in USA. 1007315R0 September 2018

CHEST NETWORKS

Disaster response, practice operations, transplant, women's health

Disaster Response and Global Health

Epigenetics and disasters

The configuration of the DNA bordering a gene dictates under what conditions a gene is expressed. Random errors or mutations affecting the neighboring DNA or the gene itself can affect how the gene functions. Epigenetics is an emerging field of science looking at environmental and psychosocial factors that do not directly cause mutations but still affect how genes are expressed with implications for the development and inheritance of disease. These external influences are thought to affect why some segments of DNA become accessible for protein production while other segments may not.

Disasters represent stressors with potential for epigenetic impact. Women who were pregnant during the 1998 Quebec ice storm were found to have a correlation between maternal objective stress and a distinctive pattern of DNA methylation in their children 13 years later (Cao-Lei, et al. *PLoS ONE*. 2014;9[9] e10765). Methylation is known to affect the activity of a DNA segment and how genes are expressed. Associations have also been found between the severity of hurricanes and the prevalence of autism in the offspring of pregnant women experiencing these disasters (Kinney DK, et al. *J Autism Dev Disord.* 2008;38:481).

Anthropogenic hazards may also affect the offspring of survivors as suggested by studies of civil war POWs and Dutch Hunger Winter during WW II (Costa, et al. *Proc Nat Acad Sci* 2018; 115:44; Heijmans, et al. *Proc Nat Acad Sci*. 2008;105[44]: 17046-9).

Epigenetics represents an area for additional research as natural and man-made disasters increase.

Omesh Toolsie, MBBS
Steering Committee Fellow-in-Training

Practice Operations

Medicare Competitive Bidding Program update

Medicare's Competitive Bidding Program (CBP), mandated since 2003, asks providers of specific durable medical equipment (including oxygen) to submit competing proposals for services. The best offer is then awarded a 3-year contract. Recently, several reforms to CBP have been proposed. The payment structure has changed to "lead-item pricing," where a single bid in each category is selected and payment amounts for each product are then calculated based on pricing ratios and fee schedules (CMS DMEPOS Competitive Bidding). This is in contrast to the prior method of

Dr. Dempsey

Dr. Sisk

median pricing, which caused financial difficulty and access concerns (Council for Quality Respiratory Care. The Rationale for Reforming Medicare Home Respiratory Therapy Payment Methodology. 2018). Budget neutrality requirements should relax, and oxygen payment

Continued on following page

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of life, in contrast to lack of effect of CPAP or ASV in this domain. Regarding side effects, 138 (91%) of 151 patients had no serious-related adverse events at 12 months. Seven (9%) cases of related-serious adverse events occurred in the control group and six (8%) cases were reported in the treatment group.—3.4% needed lead repositioning, a rate which is like that of cardiac implantable devices. Seven patients died (unrelated to implant, system, or therapy), four deaths (two in treatment group and two in control group) during the 6-month randomization period when neurostimulation was delivered to only the treatment and was off in the control group, and three deaths between 6 months and 12 months of follow-up when all patients received neurostimulation. Of 73 patients in the treatment group, 27 (37%) reported nonserious therapy-related discomfort that was resolved with simple system reprogramming in 26 (36%) patients but was unresolved in one (1%) patient.

Long-term studies have shown sustained effects of PNS on CSA with improvement in both sleep metrics and QOL, as measured by the Minnesota Living with Heart Failure Questionnaire (MLWHF) and patient global assessment (PGA). Furthermore, in the subgroup of patients with concomitant heart failure with LVEF ≤ 45%, PNS was associated with both improvements in LVEF and a trend toward lower hospitalization rates (Costanzo, et al. *Eur J Heart Fail.* 2018; doi:10.1002/ejhf.1312).

Several issues must be emphasized. One advantage of PNS is complete adherence resulting in a major reduction in apnea burden across the whole night. Second, the mechanism of action prevents any potential adverse consequences related to increased intrathoracic pressure. However, the cost of this therapy is high, similar to that of hypoglossal nerve stimulation. Large scale, long-term studies related to mortality are not yet available, and continued research should help identify those patients most likely to benefit from this therapeutic approach.

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Continued from previous page

structures improve. These proposed changes also include improved coverage of liquid oxygen and addition of home ventilator supplies.

However, effective January 1, 2019, all CBP is suspended through CMS. During the anticipated 2-year gap, any Medicare-enrolled supplier will be able to provide items until new contracts are awarded. Pricing during the gap period is based on a current single price plus consumer price index. These changes will impact CHEST members and their patients moving forward. During the temporary gap period, some areas are seeing decreased accessibility of some DME due to demand. Once reinstated, the changes to the oxygen payment structure should improve access and reduce out-of-pocket costs. The Practice Operations NetWork will continue to provide updates on this topic as they become available.

Timothy Dempsey, MD, MPH
Steering Committee Fellow-in-Training

Megan Sisk, DO
Steering Committee Member

Transplant

Medicare Part D plans can deny coverage of select immunosuppressant medications in solid organ transplant recipients

An alarming problem has emerged with some solid organ transplant recipients experiencing immunosuppressant medication claim denials by Medicare Part D plans. Affected patients are those who convert from some other insurance (ie, private insurance or state Medicaid) to Medicare after their transplant and, therefore, rely on Medicare Part D for immunosuppressant drug coverage.

Insurance companies that offer Medicare Part D plans must follow the rules described in the Medicare Prescription Drug Benefit Manual.[1] Although the Manual mandates that all immunosuppressant medications are on plan formularies, Part D plans are only required to cover immunosuppressant medications when used for indications approved by the Food and Drug Administration (FDA) or for off-label indications supported by the Centers for Medicare & Medicaid Services (CMS)-approved compendia (Drugdex® and AHFS Drug Information®).

Dr. McDermott

A recent study examining the extent of the problem demonstrated non-renal organ transplant recipients are frequently prescribed and maintained on at least one medication vulnerable to Medicare Part D claim denials at 1 year posttransplant (lung: 71.1%; intestine: 39.7%; pancreas: 36.8%; liver: 19.7%; heart: 18.5%).[2] Lung transplant recipients are most vulnerable since no immunosuppressant is FDA-approved for use in lung transplantation, and CMS-approved compendia only support off-label use for tacrolimus and cyclosporine in this population. Therefore, mycophenolate mofetil, mycophenolic acid, azathioprine, everolimus, and sirolimus are vulnerable to denial by Medicare Part D plans when used in lung transplant recipients. Over 95% of lung transplant recipients are maintained on an anti-metabolite, with the majority (88%) maintained on mycophenolate, so this is frequently impacted.[2,3] While the transplant community is aware of this issue and has begun work to correct it, it has yet to be solved.[2,4] In the meantime, if transplant recipients have been denied for this off-label and off-compendia reason, and appeals of those decisions have also been denied, options for obtaining the denied immunosuppressant medication include discount programs, foundation/grant funding, and industry-sponsored assistance programs.

Jennifer K. McDermott, PharmD
NetWork Member

1. Prescription Drug Benefit Manual. Centers for Medicare & Medicaid Services. Chapter 6: Part D Drugs and Formulary Requirements. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf

2. Potter LM et al. Transplant recipients are vulnerable to coverage denial under Medicare Part D. *Am J Transplant.* 2018;18:1502.

3. Valapour M et al. OPTN/SRTR 2016 Annual Data Report: Lung. *Am J Transplant.* 2018;18 (Suppl 1): 363.

4. Immunusuppressant Drug Coverage Under Medicare Part D Benefit. American Society of Transplantation. Available at: www.myast.org/public-policy/key-position-statements/immunosuppressant-drug-coverage-under-medicare-part-d-benefit.

Women's Health

Cannabis use affects women differently

As we enter an era of legalization, cannabis use is increasingly prevalent. Variances in the risks for women and men have been observed. For most age groups, men have higher rates of use or dependence on illicit drugs than women. However, women are equally likely as men to progress to a substance use disorder. Women may be more susceptible to craving and relapse, which are key phases of the addiction cycle. A study on use among adolescents concluded there was preliminary evidence of a faster transition from initiation of marijuana use to regular use in women, when compared with men (Schepis, et al. *J Addict Med.* 2011;5[1]:65).

Dr. Rajagopal

Research studies suggest that marijuana impairs spatial memory in women more so than in men. Studies have suggested that teenage girls who use marijuana may have a higher risk of brain structural abnormalities associated with regular marijuana exposure than teenage boys (Tapert, et al. *Addict Biol.* 2009;14[4]:457).

A study published in *Psychoneuroendocrinology* showed that cannabinoid receptor binding site densities exhibit sex differences and can be modulated by estradiol in several limbic brain regions. These findings may account for the sex differences observed with respect to the effects of cannabinoids (Riebe, et al. *Psychoneuroendocrinology.* 2010;35[8]:1265).

Further research is needed to expand our understanding of the interactions between cannabinoids and sex steroids. Detoxification treatments tailored toward women and men with cannabis addiction show a promising future and necessitate further research.

Anita Rajagopal, MD
Steering Committee Member

CHEST updates guidelines on PAH

The American College of Chest Physicians® (CHEST) has published updates to the evidence-based guidelines on therapy for pulmonary arterial hypertension (PAH). In the latest evidence-based guideline, Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report, experts provide 78 evidence-based recommendations for appropriate use in treating patients with PAH.

"New recommendations and ungraded consensus-based statements were developed in this update based on new studies that were published since the 2014 guidelines. In addition, an evidence-based and consensus-driven treatment algorithm was created to guide the clinician through an organized approach to management," says CHEST Pulmonary Arterial Hypertension Guidelines Committee Co-Chair, Deborah Jo Levine, MD, FCCP.

As part of the guideline development process, the panel updated the systematic review on the same clinical questions and criteria. Based on the results of the systematic review, the panel developed two new recommendations about pharmacologic therapy for PAH:

- For treatment-naive patients with PAH who are World Health Organization (WHO) functional class II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD).
- For stable or symptomatic patients with PAH on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD.

The complete guideline article is free to view in the Online First section (https://journal.chestnet.org/article/S0012-3692(19)30002-9/fulltext) of the journal *CHEST*®.

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BACTERIA

Semi-Quantitative Bacteria

Acinetobacter calcoaceticus-baumannii complex
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae group
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

ATYPICAL BACTERIA

Qualitative Bacteria

Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

VIRUSES

Adenovirus
Coronavirus
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza B
Parainfluenza Virus
Respiratory Syncytial Virus

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KPC
NDM
OXA-48-like
VIM

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CTX-M

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