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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Justin Sumner/University of Kentucky College of Public

Dr. Donna K. Arnett said the new guideline combines ACC and AHA recommendations and acknowledges the importance of social settings of individual patients.

CV disease prevention guide adds social determinants of health

BY MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – The first medical society guideline to comprehensively address all facets of primary prevention of cardiovascular disease put special emphasis on a team-based approach that takes into account each person's social determinants of health. The guideline substantially dialed down prior recommendations on aspirin for primary prevention by calling for no use in people older than 70 years and infrequent use in those 40-70 years old.

The American College of Cardiology and the American Heart Association released their 2019 guideline on the primary prevention of cardiovascular disease during the annual meeting of the American College of Cardiology (J Amer Coll Cardiol. 2019 Mar 17. doi: 10.1016/j.jacc.2019.03.010).

The guideline is a "one-stop shop" that pulls together existing recommendations from the two organizations and combines it with some new recommendations that address issues such as aspirin prophylaxis, and the social setting of each person, said Donna K. Arnett, PhD, professor of epidemiology at the University of Kentucky, dean of the university's College of Public Health, and co-chair of the guideline writing panel.

"We made the social determinants of health front and center. With many people, clinicians

CV PREVENTION // *continued on page 4*

Immunotherapy gaining ground for peanut allergy

BY MICHELE G. SULLIVAN
MDedge News

Immunotherapy is showing success in treating a condition that is both dangerous to millions and on the rise: peanut allergy.

James Baker, MD, a specialist in pediatric allergy and immunology, at Providence Health & Services, Lake Oswego, Ore., has embraced an innovative immunotherapy approach to peanut allergy in his clinic. He and his team have successfully treated several hundred children with a carefully constructed, evidence-based, and monitored protocol of incremental desensitization. Dr. Baker and his colleagues who take this approach will have plenty of patients in the future if the current trend in the development of peanut allergy continues.

Perception vs. reality

At the 2017 meeting of the American Academy of Allergy, Asthma, and Immunology, pediatric allergy specialist Ruchi Gupta, MD, of Northwestern University, Chicago, who presented the results of a 1-year survey of about 53,000 U.S. households, suggested that peanut allergies in kids had jumped close to 21% since 2010 (Ann Allergy Asthma Immunol. 2017 doi: 10.1016/j.anai.2017.08.060).

PEANUT ALLERGY // *continued on page 8*

INSIDE HIGHLIGHT

PULMONARY PERSPECTIVES®

Social media for physicians: Strong medicine or snake oil?

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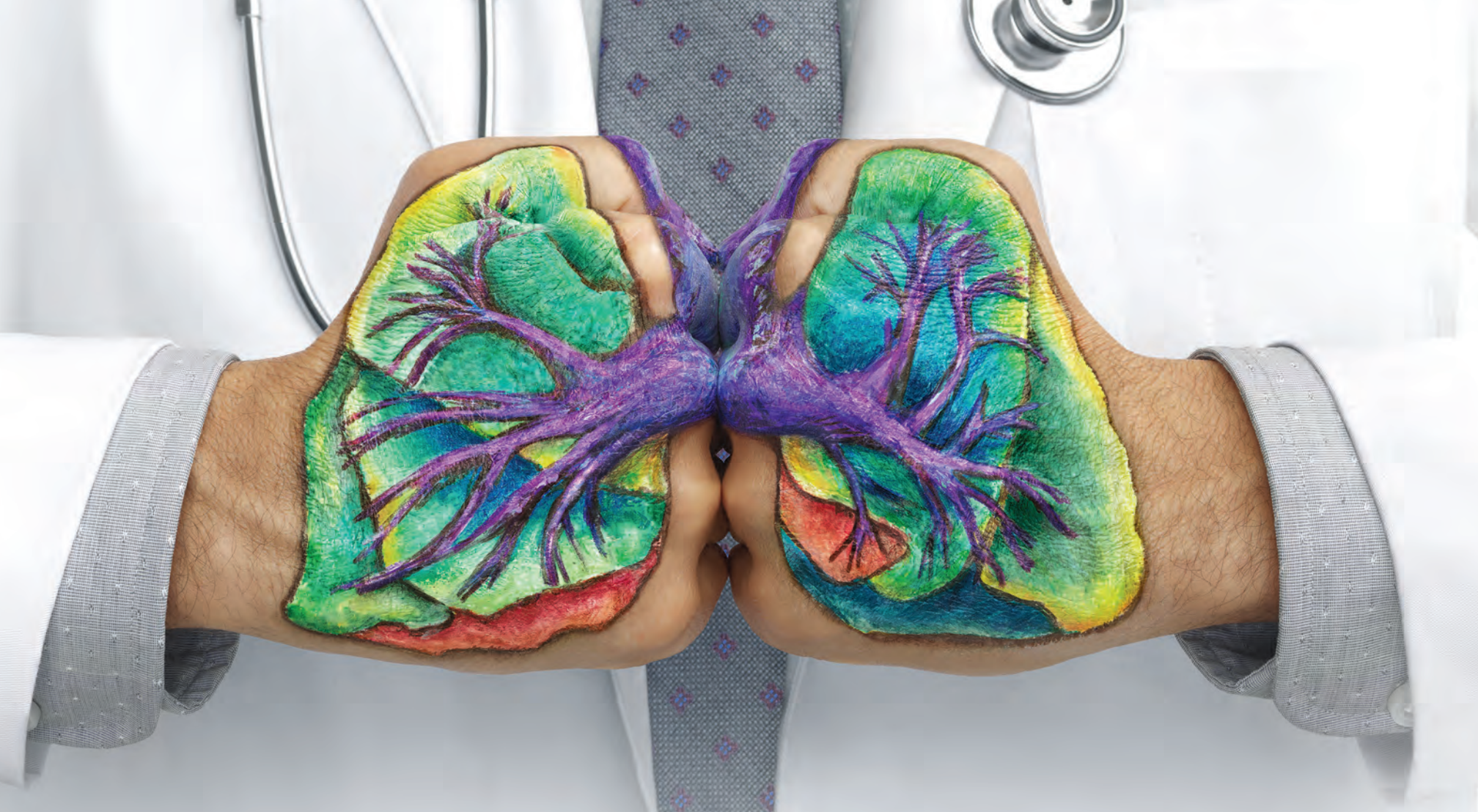

Indication

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

CV prevention guideline pulls back prior advice on aspirin use // *continued from page 1*

don't ask whether they have access to healthy foods or a way to get to the pharmacy. Asking about these issues is step one" toward helping people address their social situation, Dr. Arnett said while introducing the new guideline in a press briefing. The guideline recommends that clinicians assess the social determinants for each person treated for cardiovascular disease prevention using a screening tool developed by the U.S. Centers for Medicare & Medicaid Services and made available by the National Academy of Medicine (NAM Perspectives. 2017. doi:10.31478/201705b).

"No other guideline has highlighted the social determinants of health," noted Erin D. Michos, MD, associate director of preventive cardiology at Johns Hopkins Medicine in Baltimore, and a member of the guideline-writing panel. Other overarching themes of the guideline are its emphasis on the need for a team of clinicians to deliver all the disparate and time-consuming facets of care needed for comprehensive primary prevention of cardiovascular disease, and its call for a healthy lifestyle throughout life as foundations

Esbriet® (pirfenidone) tablets 267 mg 801 mg

Rx only

BRIEF SUMMARY

The following is a brief summary of the full Prescribing Information for ESBRIET® (pirfenidone). Please review the full Prescribing Information prior to prescribing ESBRIET.

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. In some cases these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

5.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

5.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions (5.1)]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Disorders *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

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.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials

ESBRIET® (pirfenidone)

(Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Table 2. Adverse Reactions Occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥5 to <10% of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during

Dr. Michos

"No other guideline has highlighted the social determinants of health," noted Erin D. Michos, MD, associate director of preventive cardiology at Johns Hopkins Medicine in Baltimore, and panel member.

for prevention, Dr. Michos said in a video interview.

With 48 recommendations, the guideline also deals with prevention issues such as a healthy diet and body mass, appropriate control of diabetes, smoking cessation, and control of blood pressure and cholesterol. The writing committee took the cholesterol and blood pressure recommendations directly from recent guidelines from the ACC and AHA in 2017 (blood pressure: J Amer Coll Cardiol. 2018 May;71[19]:e177-248) and 2018 (cholesterol: Circulation. 2018 Nov 10.doi: 10.1161/CIR.0000000000000625).

The other major, new recommendations in the guideline deal with aspirin use for primary prevention, which recently underwent a shake up with publication of results from several studies that showed less cardio-

Mitchel L. Zoler/MDedge News

Dr. Khera

Aspirin is appropriate "generally no, occasionally yes," said Amit Khera, MD, guideline-panel member, and professor of medicine at the University of Texas Southwestern Medical Center in Dallas.

vascular benefit and more potential bleeding harm from routine aspirin prophylaxis than previously appreciated. Among the most notable of these reports, which led to a class III recommendation – do not use – for aspirin in people more than 70 years old came from the ASPREE (Aspirin in Reducing Events in the Elderly) study (New Engl J Med. 2018 Oct 18;379[16]:1519-28). For those 40-70 years old, the recommendation is class IIb, worded as "might be considered for select adults."

"Generally no, occasionally yes," is aspirin appropriate for people in this age group, notably those at high risk for cardiovascular disease and also at low risk for bleeding, explained Amit Khera, MD, a guideline-panel member, and professor of medicine and director of preventive cardiology at the University of Texas Southwestern Medical Center in Dallas.

As a guideline for primary prevention, a prime target audience is primary care physicians, who would need to be instrumental in apply-

Continued on following page

ESBRIET® (pirfenidone)

ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.4 in full Prescribing Information]*.

Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration section 2.4 in full Prescribing Information]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2 CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risks for major birth defects and miscarriage. In animal reproduction studies, pirfenidone was not teratogenic in rats and rabbits at oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults *[see Data]*.

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

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. In these studies, pirfenidone at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. Prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from ESBRIET or from the underlying maternal condition.

Data

Animal Data

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production.

ESBRIET® (pirfenidone)

8.4 Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.6 Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*.

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

8.7 Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration section 2.3 in full Prescribing Information]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*, which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

10 OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

17 PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions (5.1)]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.3)]*.

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET *[see Clinical Pharmacology section 12.3 in full Prescribing Information]*.

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Distributed by:
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Continued from previous page

ing the guideline. But the guideline recommendations released by the ACC and AHA for blood pressure management in 2017 were not accepted by U.S. groups that represent primary care physicians, the American College of Physicians, and the American Academy of Family Physicians.

Dr. Gulati

John J. Warner, MD, an interventional cardiologist, executive vice president for health system affairs at UT Southwestern, and president of the AHA when the blood pressure guideline came out said that the ACC and AHA "learned some lessons" from the blood pressure experience. The societies responded this time around by "trying to view the document through as many lenses as possible" during the peer review process, Dr. Warner said during the press conference.

Mitchel L. Zoler/MDedge News

Dr. John J. Warner

"I don't think the new guideline will be seen as anything except positive," commented Martha Gulati, MD,

"I don't think the new guideline will be seen as anything except positive," said Martha Gulati, MD, professor of medicine and chief of cardiology at the University of Arizona in Phoenix.

professor of medicine and chief of cardiology at the University of Arizona in Phoenix. Collecting all the cardiovascular disease recommendations for primary prevention in one document "helps clinicians access the information easily and helps patients see the big picture," said Dr. Gulati, who was not involved in the guideline's writing or review. She especially applauded the recommendations to assess each person's social determinants of health, the team-care approach, and the recommendations dealing with diet and other aspects of a healthy lifestyle. "This was a perfect time" to bring together the existing blood pressure and cholesterol guidelines, the new guidance on aspirin use, and the other recommendation in a single document, she said in an interview.

Dr. Arnett, Dr. Michos, Dr. Khera, Dr. Warner, and Dr. Gulati had no disclosures.

mzoler@mdedge.com

SOURCE: Arnett DK et al. J Amer Coll Cardiol. 2019 Mar 17.doi: 10.1016/j.jacc.2019.03.010.

Primary prevention guideline: The top 10 takeaways

1. Most importantly, advise patients to maintain healthy lifestyle throughout life.
2. Use team-based care, and evaluate each person's social determinants of health to inform management.
3. Perform a 10-year atherosclerotic cardiovascular disease risk estimation on adults age 75 years or younger.
4. Advise patients to have a healthy diet and maintain normal weight.
5. Advise patients to engage in physical activity.
6. Manage type 2 diabetes appropriately.
7. Advise patients to stop smoking tobacco.
8. Prescribe aspirin infrequently for primary prevention.
9. Prescribe statin treatment appropriately to reduce risk and low-density lipoprotein cholesterol levels.
10. Manage patients' blood pressure to recommended levels, generally less than 130/80 mm Hg.

mzoler@mdedge.com

SOURCE: Arnett DK et al. J Amer Coll Cardiol. 2019 Mar 17.doi: 10.1016/j.jacc.2019.03.010.

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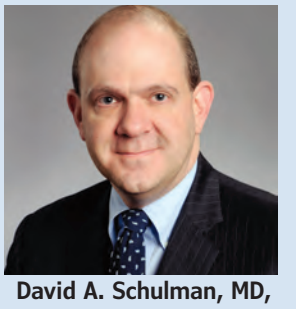

David A. Schulman, MD, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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February *CHEST Physician* story on LDCT screening complication risk: Further reflections

We received several emails from our engaged readership about one of our front-page stories from the February issue. In brief, there were concerns raised about how CHEST Physician characterized the findings of the recent study by Huo et al. in JAMA Internal Medicine. On my repeat review of our story and the Huo manuscript, as well as several conversations with content experts both within and outside of CHEST, I agree that we did mischaracterize the findings in our write-up.

While the study was not necessarily poorly conducted, there were some methodological concerns that deserved more careful consideration before putting the findings into our publication. *CHEST Physician* Editorial Board member M. Patricia Rivera, MD, FCCP, and past CHEST President Gerard A. Silvestri, MD, MS, FCCP, have kindly put together a brief discussion of the potential problems with this paper.

For those of you who took the time to write in, thanks so very much!

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

The cover story of the February 2019 edition of *CHEST Physician* titled "In real-world setting, LDCT screen is linked to high complication risk" erroneously interpreted a study by Huo and colleagues recently published in JAMA Internal Medicine. The cover story states that "the study included 174,702 individuals who underwent an invasive diagnostic procedure as a result of abnormal findings on lung cancer screening and 169,808 control subjects," "the rates of complications associated with diagnostic procedures following LDCT for lung cancer screening were substantially higher than the rates reported in clinical trials of LDCT" and that "the findings emphasize the importance of discussing the risk of adverse events and cost as part of the shared decision-making process before LDCT screening."

One wonders if the data reported by Huo and colleagues was skewed by the lens it was presented through or by the lens through which it was interpreted. Let us first elucidate that the study by Huo and colleagues titled "Complication Rates and Downstream Medical Costs Associated with Invasive Diagnostic Procedures for Lung Abnormalities in the Community Setting" was NOT a study of patients who underwent LDCT for lung cancer screening but rather a retrospective, database cohort study from 2008-2013 of patients within the age eligible for screening (age 55 to 77) WITHOUT lung cancer, who underwent similar invasive diagnostic procedures as those performed in the NLST in non–protocol-driven community practices.

Huo et al. hypothesized that the rates of complications after invasive diagnostic procedures observed among screen-eligible patients in the general population would be higher than those reported in the NLST and tested their hypothesis by estimating the complication rate of common invasive diagnostic procedures using data from a database of procedure codes. The database did not however, provide the clinical condition or indication for the procedures, define the number of procedures required to achieve a diagnosis, or define what was the most invasive procedure performed.

The authors followed patients for 1 year after their procedure and reported any complication that occurred during that period as related to that procedure. This is not the standard in reporting complications from diagnostic bronchoscopic or radiologic procedures (usually occur within 24-48 hours, or maybe days) or thoracic surgery (30-90 days). As a significant number of the complications reported in the NLST were cardiac, it would be atypical to consider a cardiac complication occurring 1 year after an invasive diagnostic procedure as a complication related to the procedure.


Chainarong Prasertthai/Getty Images

Although the results of the study by Huo and colleagues may not be representative of complications from invasive diagnostic procedures in patients undergoing lung cancer screening, they do show that diagnostic procedures performed in the inpatient and outpatient setting for any pulmonary abnormalities (nodules, masses, adenopathy, infiltrates) are associated with a high risk of complications. In an era of advanced technologies and an increasing aging and chronic critically-ill population, clinicians need to carefully appraise the risks that may be incurred following a diagnostic procedure for a pulmonary lesion and equally, the benefit and diagnostic yield of the procedure.

Multidisciplinary discussions, particularly in high-risk patients, can provide guidance to clinical decision-making regarding which procedure will be the least invasive, safest, and most likely to render a diagnosis for the individual patient.

Furthermore, we need to take into account that complication rates following procedures are likely higher in centers with a low volume of diagnostic procedures or the inability to provide a less-invasive procedure that can still provide a diagnosis.

Although it is easy to be critical of large database analyses because of the inherent limitations associated with constructing cohorts that can provide meaningful data, we should not ignore the trends outlined in this article, particularly as the size of the cohort is substantial.

One cannot argue about the importance of discussing the risk of potential complications and cost as part of the shared decision-making process before LDCT screening, but the increased rate of complications reported by Huo et al. should not be interpreted as the complication rate from lung cancer screening in real-world setting, for this is inaccurate and has potential to create additional barriers in lung cancer screening, already beset by barriers on multiple levels. Moreover, we must emphasize that discussions of potential risks and cost from diagnostic pulmonary procedures should not be isolated to lung cancer screening.

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Peanut allergy – choosing the right patients

// continued from page 1

Children were experiencing more allergic reactions to other foods too. Allergy to tree nuts increased 18% from 2010, when data were last collected, and allergy to shellfish increased 7%.

The data support what parents and clinicians have been anecdotally reporting for years now: Food allergies in children are on the rise and have been for 2 decades.

A pivotal trial introduced the notion of the benefit of early food introduction. Conducted in the United Kingdom, LEAP (Learning Early About Peanut Allergy) randomized 640 infants with severe eczema, egg allergy, or both, to either consume or avoid peanuts until 60 months of age. Among the 530 who initially had negative skin-prick peanut testing, peanut allergy developed in 13.7% in the avoidance group and 1.9% in the consumption group, a highly statistically significant difference (*P* less than .001).

The protocol

In 2008, a group at Duke University, in Durham, N.C., headed by A. Wesley Burks, MD, published the first peanut oral immunotherapy (OIT) protocol (J Allergy Clin Immunol. 2009 Aug;124:286-91.e6). Tested in 28 children with a mean age of 5 years, the protocol consisted of three phases. On the initial escalation day, children started out with 0.1 mg of peanut protein, doubling the dose every 30 minutes as tolerated until a maximum dose of 50 mg, for a total ingestion of 99 mg. Next, there was an at-home build-up phase between appointments consisting of a dose escalation of 25 mg every 2 weeks until children reached 300 mg. Finally, the home-maintenance phase was a daily ingestion of 300 mg of peanut protein, the equivalent of about one peanut.

Almost all of the children experienced some reaction on the first day, mostly respiratory and gastrointestinal symptoms and itching. The risk of reaction decreased in each dosing phase. There were only a few serious reactions during the 8-week trial, with two children requiring epinephrine during their home build-up phase.

Dr. Baker started treating patients soon after the trial appeared, basing his protocol on the Duke study. Since then, he and his assistant, Marianne Paul, have treated about 800 children with peanut, wheat, egg, soy, seed, and tree nut allergies. The team focused on these foods because they are the hardest to avoid in everyday life. Peanut allergy, however, "is the most common and the most vicious, and the one that causes the most kids to need emergency care."

Portland Photography

Marianne Paul and Dr. James Baker (right)

Ms. Paul prepares and administers the allergens, and medical staff monitor children for several hours after each exposure. She mixes peanut flour with grape juice or another liquid and administers it in increasing doses. The first visit takes several hours, beginning with skin-prick testing for a wide variety of food allergens. Then the child gets an initial dose of 0.25 mg of peanut flour. The first visit usually includes a few dose escalations, each one a doubling of the previous, until there is a mild reaction or the dose reaches 10 mg. The final goal is 4 g by 1 month, although not every child can get to that amount, Dr. Baker said.

Between the weekly visits, parents give subthreshold doses of the allergen every day, with a 1-hour observation period afterward. They are well educated in the process, have an EpiPen at the ready, and know they can call Ms. Paul at any time of the day or night for guidance.

There are also strict controls on any activities or illnesses that might rev up the immune system: No exercise for an hour before or after the dose, no hot baths or outside activity in hot weather, and strict asthma control for children with that disorder. The dose is usually reduced or held if a child gets a fever or any kind of illness, and also during vaccinations.

Choosing the right patients and parents

"It's so important to choose the right patients, and also the right parents. They all have to be extremely motivated." Dr. Baker said.

Age is a critical factor, too. Younger immune systems are more malleable, but preverbal children can't communicate well enough to describe their reactions. The ideal age, Dr. Baker said is 4-8 years old. By the time many parents enter Dr. Baker's office, they're stuck in "helicopter mode," in a constant state of worry about accidental allergen exposure. But they're usually extremely motivated to stick with the program, especially when they learn that the incidence of serious adverse events is very, very low – about 4% in a case series Dr. Baker and Ms. Paul published, along with allergists at four other practices (J Allergy Clin Immunol Pract. 2014 Jan-Feb;2[1]:91-6).

The paper reviewed reaction and success rates in 352 children treated for peanut allergy. In all, they received 240,351 doses of peanut, peanut butter, or peanut flour. Most children experienced reactions during the treatment, but the majority were mild and transient (itching, rash, mild wheezing treated with bronchodilator). Overall, 85% of the children were able to reach the target maintenance dose.

Immunotherapy products in the pipeline

Results of a potentially pivotal phase 3 study were just released. PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization) randomized 551 adults and children with peanut allergy to AR101 or placebo for 12 months (Clinicaltrials.gov identifier: NCT02635776). Subjects had a 1-day initial dose escalation from 0.5 mg to 6 mg. This was followed by dose increases every 2 weeks, from 3 mg to 300 mg, and a 24-week maintenance phase with a 300-mg target.

At the end of the study, 67.2% in the active arm and 4% in the placebo arm were able to eat the target dose of at least 600 mg of peanut protein, without a consumption-limiting symptom.

Dr. Baker is a PALISADE coinvestigator, but he expresses a tempered view of the product, which is essentially the same thing he uses in his clinic. The results of PALISADE weren't as good as those he and his colleagues achieved in their clinical case review. He predicted that the approved treatment will be substantially more expensive than using food-grade peanuts.

The peanut desensitization protocol is absolutely not a one-person show, Dr. Baker said. Any practice that wants to enter the field has to provide 24-7-365 phone support, advice, and emergency counseling. "It's part art and part science," Dr. Baker said.

"I am happy they are [conducting trials]," Dr. Baker said. "But it's costing millions of dollars, and it's only a peanut."

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VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: Like most baby-boomers, I grew up eating peanut butter. Every day. None of my friends had peanut allergies. As a young resident in adult internal medicine in the 1980s, I had heard about peanut allergies but had never seen a case. Was it a common problem?

Decades passed. At a festive family gathering at my house, my adolescent son innocently ate a couple of peanuts from one of many dishes of holiday treats. Fifteen minutes later, he had fulminant urticaria, shortness of breath, and wheezing. Our holiday party was turned into a medical emergency event.

The scenario had a happy ending. Well, mostly happy. My son's life includes his constant companions: epinephrine auto-injectors and anxiety about the ingredients in his next meal. There are special precautions made at his college dormitory. He minors in Chinese and loves the language; but is fearful of travel abroad for study because of his severe allergy and the attendant potential problems with cultural food choices, precise expression of his needs, and availability of emergency medical treatment.

Take it from a parent: The peanut allergy epidemic is real. Treatments such as desensitization allowing peanut allergy sufferers to have a better, worry-free life, would be a welcome advance.

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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.

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Revatio® sildenafil 20 mg tablets

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

^includes peripheral edema

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

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

Nervous system Seizure, seizure recurrence.

Subcutaneous immunotherapy appears dangerous for patients with severe, uncontrolled asthma

BY MITCHEL L. ZOLER
MDedge News

SAN FRANCISCO – Asthma that's severe and uncontrolled when a patient receives subcutaneous immunotherapy appears to be the "major factor" causing higher-grade systemic reactions or death from this treatment, David I. Bernstein, MD, said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

While that was Dr. Bernstein's top take-home message on how to optimize tolerability of subcutaneous immunotherapy (SCIT), a few other empiric rules have also emerged from his ongoing analysis of survey results from the AAAAI/American College of Allergy, Asthma, and Immunology SCIT surveillance study. The study began tracking the safety of SCIT in 2008 through annual surveys sent to members of either of these two allergy societies. By early 2019, the surveys had gathered data from more than 55 million office visits for SCIT, with responses from roughly 200-500 allergy practices annually, said Dr. Bernstein, professor of medicine at the University of Cincinnati.

The survey results identified seven SCIT-related fatalities over about a decade of surveillance. The most common risk factor among these cases was severe, uncontrolled asthma, prompting Dr. Bernstein to conclude that these patients should not receive SCIT. "If the asthma is well controlled, then SCIT is fine," even if it had been severe before treatment, he said in an interview.

Other factors affecting SCIT safety based on the survey results included:

- Screening patients with an asthma history for current asthma symptoms and lung function before each injection. Survey results showed that while 86% of respondents screened for symptoms, only a third also checked lung function.
- Modifying the dose or stopping SCIT injections after a severe systemic reaction. Survey results showed that more than a quarter of all systemic reactions and more than a third of grade 3 systemic reactions (severe anaphylaxis) happened following a prior systemic reaction. Dr. Bernstein called this "an important, modifiable risk factor."
- Administering SCIT only in a setting staffed to manage a possible anaphylaxis episode, and adhere to at least a 30-minute observation period. "A key step is observing for at least 30 minutes, and giving epinephrine promptly when needed; the sooner the better," Dr. Bernstein said. The percentage of practices that observe patients for at least 30 minutes has steadily improved during the decade that the survey has run.
- Modifying the SCIT dose in high-risk patients during the peak season for aeroallergens like pollen. Survey results showed that practices that did not adjust their SCIT dosages during peak pollen seasons had about double the rate of grade 3 or 4 systemic reactions, compared with practices that dialed down their dosages.
- Reducing SCIT dosages during an accelerated cluster buildup, a treatment approach that in general increases the risk for systemic reactions.


Mitchel L. Zoller/MDedge News

Dr. David I. Bernstein

Dr. Bernstein had no relevant disclosures.

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DRUG INTERACTIONS

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

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

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

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

Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary 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 pulmonary arterial hypertension (*see Clinical Considerations*). Animal reproduction studies conducted with sildenafil showed no evidence of embryo-fetal toxicity or teratogenicity at doses up to 32- and 65-times the recommended human dose (RHD) of 20 mg three times a day in rats and rabbits, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk Pregnant women with untreated pulmonary arterial hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death.

Lactation

Risk Summary 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.

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION

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

Rx only Rev. March 2018

This Brief Summary is based on the prescribing information (LAB-0313-18.0 Feb 2018).

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Poor asthma control during pregnancy raises risk of preterm delivery

BY MITCHEL L. ZOLER
MDedge News

SAN FRANCISCO – Women with poorly-controlled asthma during pregnancy had a decreased rate of live births, and among the live births had a significantly increased rate of both preterm delivery and neonatal intensive care admissions, according to a review of insurance claims data for more than 1 million American women during 2011-2015.

On the other hand, asthma severity, which the researchers inferred based on the type and amount of treatment patients received, showed essentially no link with the live birth rate, Jennifer Yland said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

"The findings add to the body of evidence that relate poor asthma control to an increased risk for pregnancy complications." explained Michael X. Schatz, MD, an allergist at Kaiser Permanente of Southern California, in San Diego, and a coauthor of the study.

Results from several prior studies had shown links between asthma and an increased rate of preterm birth, "but the larger, more generalizable population is a strength of the current findings. Results from prior studies have less frequently shown a link between asthma during pregnancy and neonatal ICU admissions," he added. "The findings strengthen the case for good asthma control during pregnancy."

For their review, Ms. Yland and her co-authors used insurance claims data from privately insured American women aged 12-55 years who were pregnant and had drug prescription records during the study period. The database included 996,861 women without an asthma diagnosis and 29,882 women diagnosed with asthma. The analysis excluded women diagnosed with chronic obstructive pulmonary disease at least twice during pregnancy.

To analyze the pregnancy outcomes by asthma severity Ms. Yland and her associates divided the asthma patients into five subgroups based on the drug regimens they were on during pregnancy as a surrogate marker of disease severity. This analysis showed no relationship between disease severity and live birth rate.

Mitchel L. Zoler/MDedge News

Jennifer Yland

The researchers also ran an analysis that divided patients into the quality of their management during pregnancy – either good or poor – based on either of two markers of poor control: filling five or more prescriptions for a short-acting beta-antagonist, or at least one exacerbation episode defined as an asthma-related emergency department visit, hospitalization, or need for oral corticosteroid treatment. By these criteria 7,135 (24%) of the pregnant women with asthma were poorly controlled. The live birth rate was 74% among women without asthma, 71% among those with well-controlled asthma, and 68% among women with poorly-controlled asthma, reported Ms. Yland, a researcher at the Harvard T.H. Chan School of Public Health in Boston.

In a multivariate analysis that adjusted for demographic differences and comorbidities, women with poorly-controlled asthma had preterm delivery a statistically significant 30% more often than did women with well-controlled asthma, and the rate of neonatal ICU admissions was a significant 24% higher in women with poorly-controlled asthma, compared with women who had well-controlled asthma. However, the rates of small-for-gestational-age infants and infants with congenital malformations was not significantly different between the well-controlled and poorly-controlled subgroups.

The finding that almost a quarter of the pregnant women in the study were poorly controlled wasn't surprising, Dr. Schatz said in an interview. In some studies as many as half the asthma patients have poor control.

The 24% rate of poor asthma control during pregnancy in the studied women is "most likely an underestimate of poor control in the general population" because the study used data from women with commercial health insurance, noted Sonia Hernandez-Diaz, MD, lead investigator for the study and professor of epidemiology at Harvard T.H. Chan School of Public Health. "More disadvantaged populations, such as pregnant women on Medicaid, tend to have worse control."

Barriers to good asthma control during pregnancy include smoking, weight gain, undertreatment, poor adherence, and viral infection. The overall approach to managing asthma during pregnancy is the same as when women are not pregnant, although certain asthma medications have a better safety record during pregnancy. "The most reassuring data exist for albuterol and inhaled steroids, particularly budesonide and fluticasone. Reassuring data also exist for the long-acting beta-agonists salmeterol and formoterol, which are combined with inhaled steroids, and for montelukast," Dr. Schatz said.

The study was funded by GlaxoSmithKline, and a coauthor of the study is a company employee. Ms. Yland had no disclosures. Dr. Schatz has received research funding from ALK, AstraZeneca, Medimmune, GlaxoSmithKline, and Merck. Dr. Hernandez-Diaz has been a consultant to Boehringer Ingelheim, Roche, and UCB, and has received research funding from GlaxoSmithKline, Lilly, and Pfizer.

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SOURCE: Yland J et al. J Allergy Clin Immunol. 2019 Feb;143(2)AB422.

New IPF diagnostic test now covered by Medicare

BY LUCAS FRANKI
MDedge News

A new genomic classifier (Envisia), produced by Veracyte, has received final Medicare local coverage determination for the diagnosis of idiopathic pulmonary fibrosis (IPF).

The test is a complement to high-resolution CT that can help differentiate IPF from other interstitial lung diseases, as more than half of patients with IPF/interstitial lung disease report being misdiagnosed at least once. The test analyzes samples obtained through transbronchial biopsy, a nonsurgical procedure commonly used in lung evaluation. It has been shown to detect usual interstitial pneumonia, a signature of IPF, with high accuracy.

Purestock/Thinkstock

The new policy was issued through the Palmetto GBA MolDx program and will go into effect on April 1, 2019, making Envisia the first commercially available test of its kind, available to the 55 million people who are currently enrolled in Medicare.

"We are pleased that the evidence supporting the Envisia classifier met the MolDx program's high standards for coverage. This important milestone will enable us to begin making the Envisia Classifier more widely available to patients with suspected IPF so that they can obtain an accurate, timely diagnosis and, in turn, appropriate treatment," Bonnie Anderson, chairman and chief executive officer of Veracyte, said in a press release.

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ONCE-DAILY
YUPELRI®
revefenacin inhalation solution
Relief that matters

FOR THE DAILY STRUGGLES OF COPD

The FIRST AND ONLY once-daily nebulized LAMA, for a full 24 hours of lung function improvement[1]

Proven 24-hour control[1]
Consistent improvement in trough FEV_1 vs placebo over 24 hours on days 84/85[1,2]

In studies 1 and 2, a prespecified exploratory analysis using serial spirometry was performed on a substudy population (YUPELRI, n=89; placebo, n=83) over 24 hours on days 84/85. In a pooled analysis, YUPELRI demonstrated consistent improvement in trough FEV_1 vs placebo over the 24-hour period.

In study 1, LS mean changes from baseline in FEV_1 ranged from 55.8 mL to 240.4 mL in the YUPELRI group, and from -113.6 mL to 59.6 mL in the placebo group. In study 2, LS mean changes from baseline in FEV_1 ranged from 19.8 mL to 148.5 mL in the YUPELRI group, and from -176.4 mL to -13.0 mL in the placebo group.

Demonstrated safety profile[1]
Refer to the Important Safety Information below for additional information

Once-daily dosing[1]
Administered with any standard jet nebulizer with a mouthpiece

Up to 100% of patients with Medicare Part B are expected to be covered
Miscellaneous J-CODE J7699*

The primary endpoint was change from baseline in trough (predose) FEV_1 at day 85 vs placebo: YUPELRI demonstrated a statistically significant difference vs placebo in Study 1 (146 mL, *P*<.0001 [YUPELRI, n=189; placebo, n=191]) and Study 2 (147 mL, *P*<.0001 [YUPELRI, n=181; placebo, n=187]).[1,2]

*Miscellaneous J-CODE listed above can be used for YUPELRI until CMS assigns a permanent code.

Indication

YUPELRI® inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Important Safety Information

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD, or for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist.

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

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Patients should be instructed to immediately consult their healthcare provider if they develop any signs and symptoms of acute narrow-angle glaucoma, including eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema.

Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. Immediate hypersensitivity reactions may occur after administration of YUPELRI. If a reaction occurs, YUPELRI should be stopped at once and alternative treatments considered.

The most common adverse reactions occurring in clinical trials at an incidence greater than or equal to 2% in the YUPELRI group, and higher than placebo, included cough, nasopharyngitis, upper respiratory infection, headache and back pain.

Coadministration of anticholinergic medicines or OATP1B1 and OATP1B3 inhibitors with YUPELRI is not recommended.

YUPELRI is not recommended in patients with any degree of hepatic impairment.

Please see Brief Summary of Full Prescribing Information on the adjacent pages.

Learn more at YUPELRIHCP.com

References: 1. YUPELRI [package insert]. Morgantown, WV: Mylan Specialty L.P.; Nov 2018. **2.** Data on file, Mylan Specialty L.P.

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Theravance® Biopharma

YUPELRI® (revefenacin)
Inhalation solution, for oral inhalation
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

YUPELRI (revefenacin) inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

WARNINGS AND PRECAUTIONS

Deterioration of Disease and Acute Episodes

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

YUPELRI is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

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

Paradoxical Bronchospasm

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

YUPELRI 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.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered.

ADVERSE REACTIONS

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

- Paradoxical bronchospasm *[see Warnings and Precautions]*
- Worsening of narrow-angle glaucoma [see Warnings and *Precautions]*
- Worsening of urinary retention *[see Warnings and Precautions]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions]*

Clinical Trial Experience

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

The revefenacin safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with revefenacin 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

YUPELRI was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with YUPELRI at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy. Patients with unstable cardiac disease, narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

Table 1 shows the most common adverse reactions that occurred with a frequency of greater than or equal to 2% in the YUPELRI group and higher than placebo in the two 12-week placebo controlled trials.

The proportion of subjects who discontinued treatment due to adverse reactions was 13% for the YUPELRI-treated subjects and 19% for placebo-treated subjects.

Table 1: Adverse Events with YUPELRI ≥2% Incidence and Higher than Placebo

	Placebo (N = 418)	YUPELRI 175 mcg (N = 395)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (4%)	17 (4%)
Infections and Infestations		
Nasopharyngitis	9 (2%)	15 (4%)
Upper respiratory tract infection	9 (2%)	11 (3%)
Nervous System Disorders		
Headache	11 (3%)	16 (4%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (1%)	9 (2%)

Other adverse reactions defined as events with an incidence of ≥1.0%, less than 2.0%, and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain and bronchitis.

52-Week Trial

YUPELRI was studied in one 52-week open-label active control (tiotropium 18 mcg once daily) trial in 1,055 patients with COPD. In this trial, 335 patients were treated with YUPELRI 175 mcg once daily and 356 patients with tiotropium. The demographic and base-line characteristics of the long-term safety trial were similar to those of the placebo-controlled 12-week studies described, with the exception that concurrent LABA or LABA/ICS therapy was used in 50% of patients. The adverse reactions reported in the long-term safety trial for YUPELRI were consistent with those observed in the placebo controlled studies of 12-weeks.

DRUG INTERACTIONS

Anticholinergics

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

Transporter-Related Drug Interactions

OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) could lead to an increase in systemic exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended *[see Clinical Pharmacology]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with YUPELRI in pregnant women. Women should be advised to contact their physician if they become pregnant while taking YUPELRI. In animal reproduction studies, subcutaneous administration of revefenacin to pregnant rats and rabbits during the period of organogenesis produced no evidence of fetal harm at respective exposures approximately 209 times the exposure at the maximum recommended human dose (MRHD) (on an area under the curve [AUC] basis) *(see Data)*.

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

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 209 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7 to 19, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 694 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Placental transfer of revefenacin and its active metabolite was observed in pregnant rabbits.

In a pre- and postnatal development (PPND) study in pregnant rats dosed during the periods of organogenesis and lactation from gestation day 6 to lactation day 20, revefenacin had no adverse developmental effects on pups at exposures up to 196 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Lactation

Risk Summary

There is no information regarding the presence of revefenacin in human milk, the effects on the breastfed infant, or the effects on milk production. However, revefenacin was present in the milk of lactating rats following dosing during pregnancy and lactation *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUPELRI and any potential adverse effects on the breastfed infant from YUPELRI or from the underlying maternal condition.

Data

Animal Data

In a PPND study revefenacin and its active metabolite were present in milk of lactating rats on lactation day 22. Milk-to-plasma concentration ratios were up to 10 for revefenacin and its active metabolite.

Pediatric Use

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

Geriatric Use

Based on available data, no adjustment of the dosage of YUPELRI in geriatric patients is necessary.

Clinical trials of YUPELRI included 441 subjects aged 65 years and older, and, of those, 101 subjects were 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 patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

The systemic exposure of revefenacin is unchanged while that of its active metabolite is increased in subjects with moderate hepatic impairment. The safety of YUPELRI has not been evaluated in COPD patients with mild-to-severe hepatic impairment. YUPELRI is not recommended in patients with any degree of hepatic impairment. *[see Clinical Pharmacology]*.

Renal Impairment

No dosage adjustment is required in patients with renal impairment. Monitor for systemic antimuscarinic side effects in COPD patients with severe renal impairment. *[see Clinical Pharmacology]*.

OVERDOSAGE

An overdose of YUPELRI may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding. In COPD patients, orally inhaled administration of YUPELRI at a once-daily dose of up to 700 mcg (4 times the maximum recommended daily dose) for 7 days was well tolerated.

Treatment of overdosage consists of discontinuation of YUPELRI along with institution of appropriate symptomatic and/or supportive therapy.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies in Sprague-Dawley rats and CD1 mice were conducted to assess the carcinogenic potential of revefenacin. No evidence of tumorigenicity was observed in male and female rats at inhaled doses up to 338 mcg/kg/day (approximately 35 times the MRHD based upon summed AUCs for revefenacin and its active metabolite). No evidence of tumorigenicity was observed in male and female mice at inhaled doses up to 326 mcg/kg/day (approximately 40 times the MRHD based on summed AUCs for revefenacin and its active metabolite).

Revefenacin and its active metabolite were negative for mutagenicity in the Ames test for bacterial gene mutation. Revefenacin was negative for genotoxicity in the *in vitro* mouse lymphoma assay and *in vivo* rat bone marrow micronucleus assay.

There were no effects on male or female fertility and reproductive performance in rats at subcutaneous revefenacin doses up to 500 mcg/kg/day (approximately 30 times the MRHD on an mg/m2 basis for revefenacin).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) with each new prescription and refill.

Not for Acute Symptoms

Inform patients that YUPELRI 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 YUPELRI without healthcare provider guidance since symptoms may recur after discontinuation.

Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue YUPELRI.

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.

Instructions for Administering YUPELRI

It is important for patients to understand how to correctly administer YUPELRI using a standard jet nebulizer [see Instructions for Use]. Instruct patients that YUPELRI should only be administered via a standard jet nebulizer. Patients should be instructed not to inject or swallow the YUPELRI solution. Patients should be instructed not to mix other medications with YUPELRI.

Patients should not inhale more than one dose at any one time. The daily dosage of YUPELRI should not exceed one unit-dose vial. Inform patients to use the contents of one vial of YUPELRI inhaled orally daily at the same time every day. Patients should throw the plastic dispensing vials away immediately after use. Due to their small size, the vials pose a danger of choking to young children.

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Daily aspirin users had fewer acute COPD flares

BY TARA HAELLE
MDedge News

FROM JOURNAL *CHEST*® ▪ Daily aspirin use could reduce the risk of acute exacerbations of chronic obstructive pulmonary disease, new data suggest.

Researchers reported the outcomes of an observational cohort study of 1,698 individuals with COPD, 45% of whom said they were taking daily aspirin at baseline. Their findings were published in Chest.

After a median follow-up of 2.7 years, aspirin users had an overall 22% lower incidence of acute COPD exacerbations compared with nonusers. This was largely accounted for by a 25% reduction in moderate exacerbations, but there was no significant difference between aspirin users and nonusers in severe exacerbations.

A similar pattern was seen after just 1 year of follow-up, with an overall 30% reduction in the incidence of exacerbations, a 37% reduction in moderate exacerbations, but no significant reduction in severe exacerbations.

"Though aspirin use has previously been linked with reduced mortality risk in patients with COPD, to our knowledge, this is the first study to investigate the association of daily aspirin use with respiratory morbidity in COPD," wrote Ashraf Fawzy, MD, of the division of pulmonary and critical care medicine at Johns Hopkins University, Baltimore, and his coauthors.

The association between aspirin use and reduced incidence of exacerbations was stronger among individuals with chronic bronchitis, which prompted the authors to suggest that future studies of aspirin in COPD should focus on participants with chronic bronchitis.

However, the association was not affected by COPD severity, emphysema presence or severity, or cardiometabolic phenotype.

Aspirin users reported better respiratory-specific quality of life than that of nonusers, including 34% lower odds of reporting moderate to severe dyspnea, and better baseline COPD health status.

"Findings of this study add to the existing literature by highlighting that aspirin use is also associated with reduced respiratory morbidity across several domains – including exacerbation risk, quality of life, and dyspnea – factors related to patient well-being and healthcare utilization," the authors wrote.

Aspirin users were more likely to be white, male, and obese, and less likely to be smokers. They had better lung function but more cardiovascular comorbidities at baseline, although the aspirin users and nonusers were matched on baseline characteristics.

Speculating on the mechanisms by which aspirin might impact COPD exacerbations, the authors noted that the drug has both systemic and local pulmonary mechanisms of action.

For example, a pathway that results in elevated levels of a urinary metabolite in patients with COPD is irreversibly blocked by aspirin. Aspirin also attenuates the elevation of inflammatory markers interleukin-6 and C-reactive protein, which are part of the inflammatory phenotype of COPD. Aspirin has been shown to reduce proinflammatory cytokines in the lung.

The authors did note that aspirin use was self-reported, so they did not have data on dosage or duration of use.

The National Institutes of Health funded the study. Six authors declared advisory board positions, research support, and other funding from the pharmaceutical sector. One author was also a founder of a company commercializing lung image analysis software. No other conflicts of interest were declared.

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SOURCE: Fawzy A et al. Chest. 2019 Mar;155(3): 519-27. doi: 10.1016/j.chest.2018.11.028.

Algorithm ruled out acute PE in pregnant women

BY ANDREW D. BOWSER
MDedge News

A diagnostic algorithm adapted for use in pregnancy safely ruled out acute pulmonary embolism in nearly 500 women with suspected pulmonary embolism enrolled in a recent prospective study, investigators are reporting.

With the adapted algorithm, there was only one deep-vein thrombosis (DVT) and no pulmonary embolism (PE) in follow-up among those women, according to the investigators, including senior author Menno V. Huisman, MD, of the department of thrombosis and hemostasis at Leiden (Netherlands) University Medical Center and his coauthors.

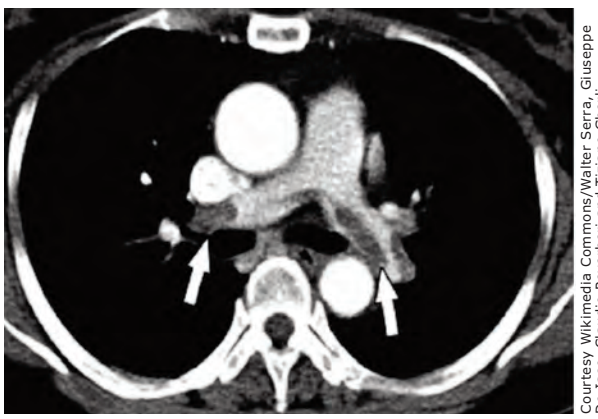
The main advantage of the algorithm is that it averted CT pulmonary angiography in nearly 40% of patients, thus sparing radiation exposure to mother and fetus in many cases, the investigators added.

"Our algorithm provides solid evidence for the safe management of suspected PE in pregnant women, with selective use of CT pulmonary angiography," Dr. Huisman and colleagues said in their March 21 report in the New England Journal of Medicine.

In a previous clinical trial, known as the YEARS study, a specialized diagnostic algorithm had a low incidence of failure in men and women with clinically suspected PE, as shown by a venous thromboembolism (VTE) rate of just 0.61% at 3 months and by use of CT pulmonary angiography that was 14 percentage points lower than with a conventional algorithmic approach.

For the current study, the investigators took the YEARS algorithm and adapted it for use in pregnant women with suspected PE presenting at 1 of 18 centers in the Netherlands, France, and Ireland.

Their adapted algorithm was based on the three criteria investigators said were most predictive in the YEARS trial, namely, clinical signs and symptoms of DVT, hemoptysis, and PE as the most likely diagnosis. Patients also underwent



Courtesy Wikimedia Commons/Walter Serra, Giuseppe De Iaco, Claudio Reverberi and Tiziano Gherli

D-dimer testing, and if they had clinical signs and symptoms of DVT, underwent compression utrasonography of the symptomatic leg.

Pulmonary embolism was considered ruled out in patients who met none of the three YEARS criteria and had a D-dimer under 1,000 ng/mL, or if they met one to three YEARS criteria and had a D-dimer under 500 ng/mL. Otherwise, patients underwent CT pulmonary angiography and started anticoagulant treatment if results of that test indicated PE.

The primary endpoint of the study was the cumulative 3-month incidence of symptomatic VTE among patients with PE ruled out by this algorithm.

Of 498 patients participating in the study, 477 (96%) had a negative result on the adapted YEARS algorithm at baseline, while 20 (4.0%) received a diagnosis of PE, according to results of the study. One patient was lost to follow-up.

Of the 477 patients with negative results, 1 patient (0.21%) had a diagnosis of symptomatic DVT over the 3 months of follow-up, investigators reported, adding that there were no PE diagnoses over the follow-up period.

That patient with the DVT diagnosis met none of the three YEARS criteria and had a D-dimer level of 480 ng/mL, and so did not undergo CT pulmonary angiography, investigators said.

In the worst-case scenario, the VTE incidence would have been 0.42%, assuming the one patient lost to follow-up would have had a VTE diagnosis over the 3-month follow-up period, they added.

"These data meet the proposed criteria for assessing the safety of diagnostic methods in VTE, even in the context of a low baseline prevalence of disease," the investigators wrote.

Overall, CT pulmonary angiography avoided potential radiation exposure-related harms in 39% of the patients, the investigators said, noting that the proportion of women avoiding the diagnostic test decreased from 65% for those evaluated in the third trimester, 46% in the second trimester, and 32% in the third.

The study was supported by unrestricted grants from Leiden University Medical Center and 17 other participating hospitals. Many authors reported financial ties to the pharmaceutical industry.

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SOURCE: van der Pol LM et al. N Engl J Med. 2019;380:1139-49.

Infective endocarditis isn't what it used to be

BY BRUCE JANCIN
MDedge News

SNOWMASS, COLO. – Infective endocarditis in 2019 is very different from the disease most physicians encountered in training, both in terms of epidemiology and clinical presentation, Patrick T. O'Gara, MD, observed at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.

The classic description of infective endocarditis provided by Sir William Osler, MD, was of a subacute bacterial infection characterized by a long latent phase of low-grade fever, back pain, weight loss, and night sweats. It was mainly a right-heart disease of younger individuals with an infected native valve, and the predominant pathogens were streptococci, Dr. O'Gara said.

Bruce Jancin/MDedge News

Dr. Patrick T. O'Gara

"I think in the current era endocarditis is more often characterized by an acute illness with toxic features in the context of adults with a high burden of degenerative diseases – for example, patients with rheumatoid arthritis or psoriatic arthritis on immunosuppressive therapy, or diabetes, end-stage renal disease, and risk factors for hospital-acquired infection. Injectable drug use is through the roof; there's a wider prevalence of cardiac implanted electronic devices, which are a wonderful place for bacteria to hide; and *Staphylococcus aureus* has certainly become the leading pathogen with regard to endocarditis in the United States, especially MRSA, often multidrug resistant," said Dr. O'Gara, professor of medicine at Harvard Medical School, Boston.

"Also, no talk about endocarditis is sufficient without paying some attention to the opioid crisis in which we find ourselves. It's one of the top three causes of death among young men in the United States, along with accidents and gun violence. No region of the country is spared. This has completely inundated our ER and hospitalist services and our inpatient cardiology services with folks who are often repeat offenders when it comes to the difficulty in being able to give up an injectable drug use habit. They have multiple infections and hospitalizations, tricuspid valve involvement, and depending upon the aggressiveness of the *Staphylococcus* organism, typically they have left-sided disease with multiple complications, including aortic regurgitation and heart failure," the cardiologist continued.

This description underscored one of Dr. O'Gara's major points about the challenges posed by infective endocarditis in contemporary practice: "Expect the unexpected," he advised. "When you've seen one case of infective endocarditis, you've seen one case of infective endocarditis."

Outcomes are 'sobering'

In the current era, outcomes are "sobering," the cardiologist noted. Infective endocarditis carries a 6-month mortality rate of 20%-25% despite early surgery being performed during the index hospitalization in up to 60% of patients, with a relatively high perioperative mortality rate of about 10%. However, the risk of reinfection occurring in a newly implanted cardiac valve is impressively low at about 2%.

Refer early for multimodality imaging and surgical consultation

Transesophageal echocardiography is valuable in assessment of the infected valve. However, when extravalvular extension of the infection is suspected and the echo assessment is nondiagnostic or indeterminate, it's time to quickly move on to advanced imaging, such as PET-CT.

The ACC/American Heart Association class I recommendations for early surgery in infected native valves haven't changed substantially in over a decade. Based largely on observational data, there is an association between early surgery and lower in-hospital mortality (Lancet. 2012 Mar 10;379[9819]:965-75).

Class IIa recommendations for native valve surgery include recurrent emboli and a persistent vegetation despite appropriate antibiotic therapy. A "very controversial" class IIb recommendation for surgery because of weak supporting data is the identification of a mobile vegetation larger than 10 mm, particularly if it's located on an anterior mitral valve leaflet, he said. If the decision is made to forgo early surgery, be sure to repeat transesophageal echocardiography on day 7-10 to reassess the size of the patient's vegetation.

"There is an association between size of vegetation and 1-year mortality, with a cut point of greater than 15 mm. Some would argue this constitutes a reasonable indication for early surgery," Dr. O'Gara noted.

The embolization rate in patients with infective endocarditis is highest during the day before presentation, the day of presentation, and through the first 2 days afterward. The rate drops precipitously within 2 weeks after initiation of appropriate antibiotic therapy. Thus, to utilize early surgery to maximum effect in order to decrease the risk of embolization, it makes sense to operate within the first several days following presentation, before antibiotics have had sufficient time to catch up with the evolving disease process.

Removal of cardiac implanted electronic devices

The guidelines are clear regarding infected pacemakers, implanted cardioverter defibrillators, and cardiac resynchronization devices: "It all needs to come out," Dr. O'Gara emphasized. That includes all leads and the generator in patients with documented infection of only one portion of the device system, as a class I, level of evidence B recommendation. Moreover, complete removal of a pacemaker or defibrillator system is deemed "reasonable" as a class IIa recommendation in all patients with valvular infection caused by *S. aureus* or fungi even in the absence of evidence of device infection.

"I think we as general cardiologists have become increasingly impressed about how sick and festering these kinds of patients can become, even when we're not able to prove that the lead is infected. The lead looks okay on transesophageal echo or PET-CT, blood cultures are negative, the valvular heart disease is really not that advanced, but several days go by and the patient is just not responding. We should have a high index of suspicion that there's an infection we cannot appreciate. But obviously, you make these difficult decisions in consultation with your electrophysiology colleagues," he added.

Know when to say 'no' to early aggressive surgery

While an aggressive early surgical approach often pays off in terms of prevention of embolic sequelae and a reduction in heart failure, the timing of surgery in the 20%-40% of patients with infective endocarditis who present with stroke or other neurologic complications remains controversial. An international group of Canadian and French cardiac surgeons and neurologists developed a useful algorithm regarding the types of neurologic complications for which early cardiac surgery is a poor idea because of the high risk of neurologic exacerbation. For example, a mycotic neuroaneurysm is grounds for postponement of cardiac surgery for at least 4 weeks (Circulation. 2016 Oct 25;134[17]:1280-92).

Dr. O'Gara reported receiving funding from the National Heart, Lung, and Blood Institute, 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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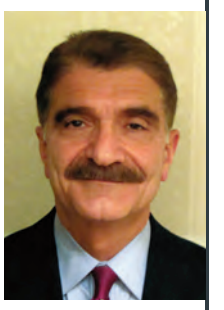
VIEW ON THE NEWS



G. Hossein Almassi, MD, FCCP, comments: In this brief overview of infective endocarditis, the author brings up some important points on the management of this deadly disease. Aggressive and early surgical intervention with radical excision and debridement of all infected tissue is the key to better surgical outcomes and survival. With the epidemic of drug addiction, clinicians are now faced with mixed organisms and gram-negative left-sided endocarditis. Unfortunately, and due to lack of adequate and appropriate rehabilitation facilities to transfer these patients to following their hospitalization, there is a high rate of recurrence and hospital readmission.

DUPIXENT®
(dupilumab) Injection
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NOW APPROVED
IN MODERATE-TO-SEVERE ASTHMA

INDICATION

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

LIMITATION OF USE

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

DUPIXENT is the **first and only dual inhibitor of IL-4 and IL-13 signaling**

IMPORTANT SAFETY INFORMATION

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

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

Visit **DUPIXENTASTHMAHCP.COM**

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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

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

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

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

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

SANOFI GENZYME

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

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

USE IN SPECIFIC POPULATIONS

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

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

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Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

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

1.2 Asthma

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

Limitation of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

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

5.3 Eosinophilic Conditions

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

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

5.6 Atopic Dermatitis Patients with Comorbid Asthma

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

5.7 Parasitic (Helminth) Infections

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Atopic Dermatitis

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

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

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

Weeks 0 to 16 (Trials 1 to 4):

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

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

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

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

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

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

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

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

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

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

Safety through Week 52 (Trial 3):

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

Asthma

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

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

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

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

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

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

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

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

Specific Adverse Reactions:

Conjunctivitis

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

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

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

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median

increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

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

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

6.2 Immunogenicity

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Atopic Dermatitis

Safety and efficacy in pediatric patients (<18 years of age) with atopic dermatitis have not been established.

Asthma

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

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

8.5 Geriatric Use

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

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

10 OVERDOSE

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

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions

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

Hypersensitivity

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

Conjunctivitis and Keratitis

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

Eosinophilic Conditions

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

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

Atopic Dermatitis Patients with Comorbid Asthma

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

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Before you refer for AFib ablation, educate your patient

BY BRUCE JANCIN
MDedge News

SNOWMASS, COLO. – Appropriate counseling before making a referral for atrial fibrillation ablation entails helping the patient understand what can realistically be expected in the way of benefit, along with instilling awareness of the warning signals heralding serious late complications, Samuel J. Asirvatham, MD, said at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.

"Who to steer toward ablation? You have to have a symptomatic patient – that's a given. For the ones who are paroxysmal, the ones with a relatively normal heart, there's a much better chance that you'll help manage their symptoms with ablation than if they have persistent or permanent AFib. Notice I do not use the word 'cure' for AFib. We talk about controlling symptoms and decreasing frequency, because the longer follow-up you have with intensive monitoring, the more you realize that patients still tend to have some AFib," explained Dr. Asirvatham, an electrophysiologist who is professor of medicine and pediatrics at the Mayo Clinic in Rochester, Minn.

The rationale for early atrial fibrillation (AFib) ablation in younger patients with troublesome symptoms of paroxysmal AFib despite pharmacologic attempts at rate or rhythm control is that it will arrest the progression from an atrial arrhythmia that has just a few triggers readily neutralized by pulmonary vein isolation to persistent AFib with a diseased heart and a multitude of arrhythmia trigger points coming from many directions.

A solid candidate for ablation of paroxysmal AFib has about a 75% likelihood of having a successful first ablation procedure, with substantial improvement in symptoms and no need for medication. Another 9%-10% will achieve marked reduction in symptom burden upon addition of antiarrhythmic agents that weren't effective before ablation.

Late complications can be deceptive

Periprocedural stroke/transient ischemic attack, tamponade, or bleeding on the table are infrequent complications readily recognized by the interventionalist. More problematic are several late complications which are often misinterpreted, with the resultant delay causing major harm.

- **Pulmonary vein stenosis.** This complication of inadvertent ablation inside the pulmonary vein manifests as shortness of breath, typically beginning about 4 weeks post ablation.

"This is very different from the shortness of breath they had with atrial fibrillation. They almost always have a cough that they didn't have before, and they may have hemoptysis. It's very important to recognize this promptly, because before it closes completely we can do an angioplasty and stent the vein with good results. But once it closes completely, it becomes an extremely complicated procedure to try to reopen that vein," according to Dr. Asirvatham.


Bruce Jancin/MDedge News
Dr. Samuel J. Asirvatham

Very often the patient's general cardiologist, chest physician, or primary care physician fails to recognize what's happening. He cited an example: He recently had a patient with a cough who was first referred to an infectious disease specialist, who ordered a bronchoalveolar lavage. The specimen grew atypical actinomycetes. That prompted a referral to thoracic surgery for an open-lung biopsy. But that procedure required cardiac clearance beforehand. It was a cardiologist who said, 'Wait – all this started after you had an ablation?'

"That patient had pulmonary vein stenosis. And, unfortunately, that complication has not gone away. Being a referral center for pulmonary vein isolation, we see just as many cases of pulmonary vein stenosis today as we did a few years ago," he said.

- **Atrial esophageal fistula.** The hallmark of this complication is onset of a plethora of what Dr. Asirvatham called "funny symptoms" more than a month post ablation. These include fever, transient ischemic attacks (TIAs), sepsislike symptoms, discomfort in swallowing, and in some cases hemoptysis.

"The predominant picture is endocarditis/TIA/stroke. If you see this, and the patient has had ablation, immediately refer to surgery to have the fistula between the esophagus and heart fixed. This is not a patient where you say, 'Nothing by mouth, give some antibiotics, and see what happens.' I can tell you what will happen: The patient will die," the cardiologist said.

- **Atrial stiffness.** This typically occurs about a month after a second or third ablation procedure, when the patient develops shortness of breath that keeps worsening.

"You think 'pulmonary vein stenosis,' but the CT scan shows the veins are wide open. Many of these patients will get misdiagnosed as having heart failure with preserved ejection fraction even though they never had it before. The problem here is the atrium has become too stiff from the ablation, and this stiff atrium causes increased pressure, resulting in the shortness of breath. Sometimes patients feel better over time, but sometimes it's very difficult to treat. But it's important to recognize atrial stiffness and exclude other causes like pulmonary vein stenosis," Dr. Asirvatham continued.

- **Gastroparesis.** This occurs because of injury to the vagus nerve branches located at the top of the esophagus, with resultant delayed gastric emptying.

"It's an uncomfortable feeling of fullness all the time. The patient will say, 'It seems like I just ate, even though I ate 8 hours ago," the electrophysiologist said. "Most of these patients will recover in about 6 months. They may feel better on a gastric motility agent, like a macrolide antibiotic. I personally have not seen a patient who did not feel better within 6-8 months."

Novel treatment approaches

"Patients sometimes will ask you, 'What is this ablation? What does that mean?' You have to be truthful and tell them that it's just a fancy word for burning," the electrophysiologist said.

Achievement of AFib ablation without radiofrequency or cryoablation, instead utilizing nonthermal direct-current pulsed electrical fields, is "the hottest topic in the field of electrophysiology," according to Dr. Asirvatham.

These electrical fields result in irreversible electroporation of targeted myocardial cell membranes, leading to cell death. It is a tissue-specific intervention, so it's much less likely than conventional ablation to cause collateral damage to the esophagus and other structures.

"Direct current electroporation has transitioned from proof-of-concept studies to three relatively large patient trials. This is potentially an important breakthrough because if we don't heat, a lot of the complications of Afib ablation will probably decrease," he explained.

Two other promising outside-the-box approaches to the treatment of AFib are autonomic nervous system modulation at sites distant from the heart and particle beam ablation without need for cardiac catheters.

"If you put electrodes everywhere in the body to see where Afib starts, it's not in the atrium, not in the pulmonary veins, it's in the nerves behind the pulmonary veins, and before those nerves it's in some other area of the autonomic nervous system. This has given rise to the notion that Afib may be an autonomic epilepsy of the heart," according to the electrophysiologist.

This concept has given rise to a completely different approach to treatment of AFib through neurostimulation. Dr. Asirvatham reported having no financial conflicts regarding his presentation, although he serves as a consultant to a handful of medical startup companies and holds patents on intellectual property, the royalties for which go directly to the Mayo Clinic.

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VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: With the aging population, clinicians are faced with an increasing number of patients with atrial fibrillation. The important point brought up by the author is the obligation of the electrophysiologist to have a frank discussion with the patient on the expected outcome of ablation and the potential for serious and life-threatening complications. The ongoing research on alternative technology for treatment of AF should be of interest to cardiologists and electrophysiologists.

ONCE-DAILY TRIPLE THERAPY

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

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

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

Please see additional Important Safety Information for TRELEGY throughout.

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

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

gsk | INNOVIVA

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

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

IMPACT *INFORMING THE PATHWAY OF COPD TREATMENT*

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

In patients with a history of COPD exacerbations

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

15%
REDUCTION in annual rate vs BREO
(*P*<0.001)

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

25%
REDUCTION in annual rate vs ANORO
(*P*<0.001)

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

ANORO is not approved for the reduction of COPD exacerbations.

STUDY DESCRIPTION[1,2]

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

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

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

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

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

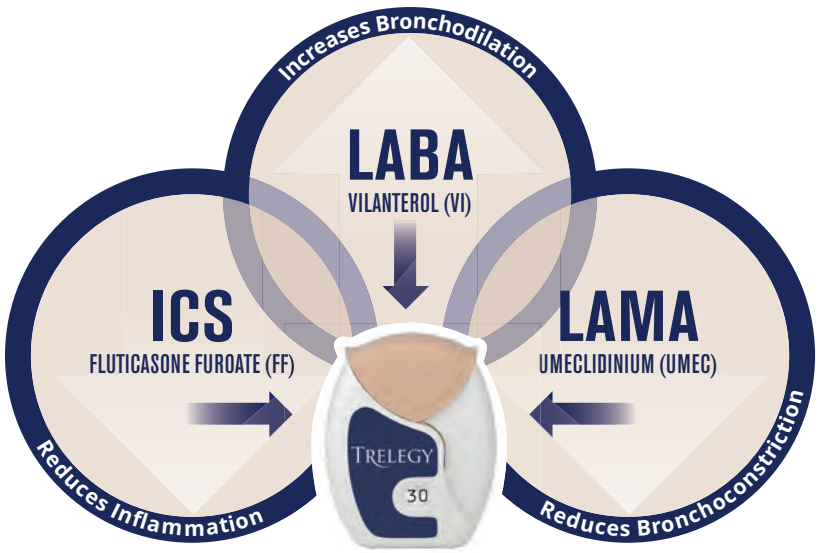
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- TRELEGY is NOT a rescue medication and should NOT be used for the relief of acute bronchospasm or symptoms. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.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

Please see additional Important Safety Information for TRELEGY throughout.

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

SIMPLIFIED DELIVERY OF TRIPLE THERAPY

3 MEDICATIONS IN 1 INHALER WITH 1 DAILY INHALATION



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

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

See additional data. Visit DiscoverTRELEGY.com

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to TRELEGY.
- Hypercorticism and adrenal suppression may occur with higher than the recommended dosage or at the regular dosage of ICS in susceptible individuals. If such changes occur, appropriate therapy should be considered.
- Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue TRELEGY and institute alternative therapy.
- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRELEGY. Discontinue TRELEGY if such reactions occur.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, TRELEGY may need to be discontinued. TRELEGY should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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

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

OR VISIT **DISCOVERTRELEGY.COM**

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- Decreases in bone mineral density have been observed with long-term administration of products containing ICS. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care prior to initiating TRELEGY and periodically thereafter.
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the long-term administration of ICS or inhaled anticholinergics. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
- Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Please see additional Important Safety Information for TRELEGY throughout.

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

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

TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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

BRIEF SUMMARY

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

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

1 INDICATIONS AND USAGE

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

Important Limitations of Use

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

5.2 Deterioration of Disease and Acute Episodes

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

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

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms.

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

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

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

5.4 Local Effects of Inhaled Corticosteroids

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

5.5 Pneumonia

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

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

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

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

5.6 Immunosuppression

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

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

5.7 Transferring Patients From Systemic Corticosteroid Therapy

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

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRELEGY. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRELEGY. Lung function (forced expiratory volume in 1 second [FEV_1]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to TRELEGY may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (eg, rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

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

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses

Continued on next page

of fluticasone furoate in TRELEGY. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with TRELEGY should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

5.10 Paradoxical Bronchospasm

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

5.11 Hypersensitivity Reactions, Including Anaphylaxis

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

5.12 Cardiovascular Effects

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

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

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

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

5.13 Reduction in Bone Mineral Density

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

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of ICS or with use of inhaled anticholinergics. TRELEGY should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (eg, eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRELEGY long term.

5.15 Worsening of Urinary Retention

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

5.16 Coexisting Conditions

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

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

Trials 1 and 2

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

Continued on next page

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

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

Trial 3 - Long-term Safety Data

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

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

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of TRELEGY with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3) of full prescribing information]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non–Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

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

8.2 Lactation

Risk Summary

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

8.5 Geriatric Use

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

In Trials 1 and 2 (coadministration trials), 189 subjects aged 65 years and older, of which 39 subjects were aged 75 years and older, were administered umeclidinium 62.5 mcg + fluticasone furoate/vilanterol 100 mcg/25 mcg. In Trial 3, 2,265 subjects aged 65 years and older, of which 565 subjects were aged 75 years and older, were administered TRELEGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

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

Fluticasone Furoate/Vilanterol

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

Umeclidinium

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

10 OVERDOSAGE

No human overdosage data has been reported for TRELEGY.

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

10.1 Fluticasone Furoate

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

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

10.2 Umeclidinium

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

10.3 Vilanterol

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use *of full prescribing information*).

Not for Acute Symptoms

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

Continued on next page

BRIEF SUMMARY

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

short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

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

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

Tell patients they should not stop therapy with TRELEGY without physician/provider guidance since symptoms may recur after discontinuation.

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

Instruct patients not to use other LABA.

Local Effects

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

Pneumonia

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

Immunosuppression

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

Hypercorticism and Adrenal Suppression

Advise patients that TRELEGY may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRELEGY.

Paradoxical Bronchospasm

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

Hypersensitivity Reactions, Including Anaphylaxis

Advise patients that hypersensitivity reactions (eg, anaphylaxis, angioedema, rash, urticaria) may occur after administration of TRELEGY. Instruct patients to discontinue TRELEGY if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use TRELEGY.

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Glaucoma and Cataracts

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

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

Worsening of Urinary Retention

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

Risks Associated With Beta-agonist Therapy

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

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FVUJRNA180004 January 2019
Produced in USA.

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

Palliative care has improved for critically ill children, but challenges remain

BY JIM KLING
MDedge News

SAN DIEGO – Palliative care among critically ill pediatric patients in the intensive care unit is highly variable across institutions, and is more common among older children, female children, and those with government insurance or at a high risk of mortality. The findings come from a retrospective analysis of data from 52 hospitals, which included ICU admissions (except neonatal ICU) during 2007-2018.

The good news is that palliative care consultations have increased, with consultations in less than 1% of cases at the start of the study and rising quickly to more than 7% in 2018.

"In the adult world, palliative care has expanded in recent decades, and I think now that it's coming to the pediatric world, it'll just continue to go up," said Siobhan O'Keefe, MD, in an interview. Dr. O'Keefe is with Children's Hospital Colorado, Aurora. She presented the study at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

More work needs to be done, she said. "We are not uniformly using palliative care for critically ill children in the U.S., and it varies across institutions. That's probably not the ideal situation," said Dr. O'Keefe. The study did not track palliative care versus the presence of board-certified palliative care physicians or palliative care fellowships, but she suspects they would correlate.

Jim Kling/MDedge News

Dr. Siobhan O'Keefe

Dr. O'Keefe called for physicians to think beyond the patient, to family members and caregivers. "We need to focus on family outcomes, how they are taking care of children with moderate disability, and incorporate that into our outcomes," she said. Previous research has shown family members to be at risk of anxiety, depression, unemployment, and financial distress.

The researchers analyzed data from 740,890 patients with 1,024,666 hospitalizations (82% had one hospitalization). They divided subjects into three cohorts, one of which was a category of patients with criteria for palliative care based on previous research (PC-ICU). The PC-ICU cohort included patients with an expected length of stay more than 2 weeks, patients receiving extracorporeal membrane oxygenation (ECMO), severe brain injuries, acute respiratory failure with serious comorbidity, hematologic or oncologic disease, metabolic disease, renal failure that required continuous renal replacement therapy, hepatic failure, or serious chromosomal abnormality. A second cohort included chronic complex conditions not found in the PC-ICU cohort (additional criteria), and a third cohort had no criteria for palliative care.

Thirty percent of hospitalizations met the PC-ICU cohort criteria, 40% met the additional cohort criteria, and 30% fell in the no criteria cohort. The PC-ICU group had the highest mortality, at 8.03%, compared with 1.08% in the additional criteria group and 0.34% in the no criteria group (*P* less than .00001).

Palliative care consultations occurred more frequently in 5-12 year olds (odds ratio 1.06; 95% confidence interval, 1.01-1.13) and in those aged 13 years or older (OR, 1.38; 95% CI, 1.3-1.46), in females (OR, 1.13; 95% CI, 1.06-1.15), and in patients with government insurance (OR, 1.23; 95% CI, 1.17-1.29). Compared with those in the no criteria cohort, PC-ICU patients were more likely to receive a palliative care consult (OR, 75.5; 95% CI, 60.4-94.3), as were those in the additional criteria group (OR, 19.1; 95% CI, 15.3-23.9).

Cross-institutional palliative care frequency varied widely among patients in the PC-ICU group, ranging from 0% to 44%. The frequency ranged from 0% to 12% across institutions for patients in the additional criteria group.

chestphysiciannews@chestnet.org

SOURCE: O'Keefe S et al. Critical Care Congress 2019, Abstract 418.

Half of children with atopic dermatitis have sleep problems

BY HEIDI SPLETE
MDedge News

Poor sleep quality, but not sleep duration, was significantly associated with active atopic dermatitis in a longitudinal study of more than 13,000 children.

The itching associated with atopic dermatitis (AD) may interfere with children's sleep, and sleep studies suggest that children with active disease are more restless at night, wrote Faustine D. Ramirez of the University of California, San Francisco, and her colleagues. Their report is in JAMA Pediatrics.

"Acute and chronic sleep disturbances have been associated with a wide range of cognitive, mood, and behavioral impairments and have been linked to poor educational performance," the researchers noted.

To determine the impact of active AD on children's sleep, the researchers reviewed data from 13,988 children followed for a median of 11 years. Of these, 4,938 children met the definition for AD between age 2 and 16 years.

Overall, children with active AD were approximately 50% more likely to experience poor sleep quality than were those without AD (adjusted odds ratio, 1.48). Sleep quality was even worse for children with severe active AD (aOR, 1.68), and active AD plus asthma or allergic rhinitis (aOR 2.15). Sleep quality was significantly worse in children reporting mild AD (aOR, 1.40) or inactive AD (aOR, 1.41), compared with children without AD. Nighttime sleep duration was similar throughout childhood for children with and without AD.

"In addition to increased nighttime awakenings and difficulty falling asleep, we found that children with active atopic dermatitis were more likely to report nightmares and early morning awakenings, which has not been previously studied," Ms. Ramirez and her associates said.

Total sleep duration was statistically shorter overall for children with AD, compared with those without AD, but the difference was not clinically significant, they noted.

The participants were from a longitudinal study in the United Kingdom in which pregnant women were recruited between 1990 and 1992. For those with children alive at 1 year, their children were followed for approximately 16 years. Sleep quality was assessed at six time points with four standardized questionnaires between ages 2 and 10 years, and sleep duration was assessed at eight time points between ages 2 and 16 years with standardized questionnaires.

The study findings were limited by several factors, including some missing data and patient attrition, as well as possible misclassification bias because of the use of parent and patient self-reports, and a possible lack of generalizability to other populations, the researchers noted.

However, the results support the need for developing clinical outcome measures to address sleep quality in children with AD, they said. "Additional work should investigate interventions to improve sleep quality and examine the association between atopic dermatitis treatment and children's sleep."

The study was funded primarily by a grant from the National Eczema Association. Ms. Ramirez disclosed a grant from the National Institutes of Health. Two other investigators received grants, one from NIH and the other Wellcome Senior Clinical Fellowship in Science. One coauthor reported receiving multiple grants, as well as paid consulting for TARGETPharma, a company developing a prospective atopic dermatitis registry.

chestphysiciannews@chestnet.org

SOURCE: Ramirez FD al. JAMA Pediatr. 2019 Mar 4. doi: 10.1001/jamapediatrics.2019.0025.

Home oxygen therapy for children: New guidelines combine limited evidence, expert experience

BY ANDREW D. BOWSER
MDedge News

Based on the very limited evidence available, an expert panel convened by the American Thoracic Society has devised a clinical practice guideline specific to children who require home oxygen therapy.

The guideline authors not only addressed specific indications for chronic lung and pulmonary vascular diseases, but also defined hypoxemia in children – noting that Medicare and Medicaid coverage determinations for home oxygen therapy in children are based on decades-old studies that lacked pediatric patients – and offer expert advice on how to wean and discontinue oxygen, when warranted.

The disease-specific recommendations on whether or not to prescribe home oxygen therapy are characterized either as strong, meaning that it's the right course of action for at least 95% of patients; or conditional, meaning it might not be right for a "sizable minority" of patients, authors explained in the guideline.

Home oxygen therapy gets a strong recommendation, for example, in patients with cystic fibrosis complicated by severe chronic hypoxemia, but gets a conditional recommendation for sickle cell disease with severe chronic hypoxemia, according to the guideline, published in the American Journal of Respiratory and Critical Care Medicine.

Regardless of strong or conditional, the recommendations were largely based on "very low-quality evidence," according to ad hoc subcommittee of the ATS Assembly on Pediatrics, cochaired by Don Hayes Jr., MD, of Nationwide Children's Hospital, Columbus, Ohio, and Robin R. Deterding, MD, of Children's Hospital Colorado, Denver.

"Despite widespread use of home oxygen therapy for various lung and pulmonary vascular diseases, there is a striking paucity of data regarding its implementation, efficacy, monitoring, and discontinuation," Dr. Hayes, Dr. Deterding, and 20 additional committee members wrote in their report.

Accordingly, the panel sought to add expert opinion and experience to the limited evidence, in the hope that it would aid clinicians in the management of complex pediatric patients, they said.

One new tool they provide, toward that end, is a definition of hypoxemia in children based on oxygen saturation as quantified by pulse oximetry (Spo_2).

Based on a review of 31 selected studies measuring oxygenation in healthy children, the expert panel defined hypoxemia (at or near sea level) as Spo_2 of 90% or lower for 5% of the recording time in children under 1 year old, and an Spo_2 of 93% or lower in older children; or alternatively, as three independent measurements of Spo_2 less than or equal to 90% in the younger children and 93% in the older children.

By contrast, an Spo_2 of less than 88% is one of the indications for funding home oxygen therapy as determined by the Centers for Medicare & Medicaid Services for both pediatric and adult patients, according to the committee.

The CMS indications derived from "seminal studies" showing that continuous oxygen therapy reduced mortality in adults with chronic obstructive pulmonary disease, they said in the guideline document.

"Despite the lack of pediatric patients in these historic studies performed over 35 years ago, the CMS coverage determination for [home oxygen therapy] is the same for pediatric patients of all ages compared with adult patients," they wrote in the report.

The committee unanimously agreed that 2 weeks of low Spo_2 was "sufficient evidence" to indicate chronic hypoxemia, their report says.

Dr. Hayes reported no relationships with relevant commercial interests, while Dr. Deterding provided disclosures related to Boehringer Ingelheim, Novartis, and Elsevier Publishing, among others. Fellow committee members provided disclosures related to Shire Pharmaceuticals, United Therapeutics, and others as listed in the clinical practice guideline document.

chestphysiciannews@chestnet.org

SOURCE: Hayes D et al. J Respir Crit Care Med. 2019 Feb 1;199(3):e5-e23. doi: 10.1164/rccm.201812-2276ST.

VIEW ON THE NEWS

More research sorely needed

It is unfortunate that, over the course of a decade, the evidence base supporting home oxygen therapy in children has not substantially changed, according to Ian Balfour-Lynn, MD, a member of the American Thoracic Society (ATS) committee that developed the clinical practice guideline.

The ATS clinical practice guideline on home oxygen therapy for children echoes conclusions reached in a 2009 guideline published by the British Thoracic Society (BTS), he wrote in The Lancet Respiratory Medicine.

Dr. Balfour-Lynn, who chaired the BTS guideline committee, said new research is sorely needed, particularly in the prevention of preterm births, which he said constitute the commonest cause of home oxygen need among children, according to the Lancet report.

In addition, a large prospective trial is needed to evaluate strategies for weaning or discontinuing oxygen, he said, noting that the ATS recommendations on weaning were almost entirely based on the expert panel's combined clinical experience.

Dr. Balfour-Lynn is a consultant in pediatric respiratory medicine at Royal Brompton Hospital, London. This summary of his opinions is based on his comments in a report that appeared March 8 in The Lancet Respiratory Medicine. He reported no relationships with commercial interests relevant to his work on the ATS clinical practice guideline.

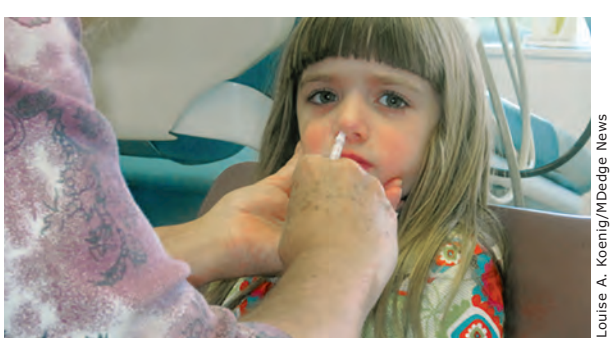
AAP updates 2019-2020 flu vaccine recommendations to include nasal spray

BY CHRISTOPHER PALMER
MDedge News

Although the American Academy of Pediatrics had cited a preference for injected flu vaccines for children during the 2018-2019 flu season, this year's recommendations say either that or the nasal spray formulation are acceptable, according to a press release. The Centers for Disease Control and Prevention has given similar guidance.

Because the spray did not work as well against A/H1N1 as the injected vaccine had during the 2013-2014 and 2014-2015 seasons, the AAP did not recommend the spray during the 2015-2016 and 2016-2017 seasons. However, in 2017 the spray's manufacturer included a new strain of A/H1N1, and new data has supported the spray's effectiveness against some strains.

The AAP recommends all children aged 6 months and older should be vaccinated, but the flu nasal spray is approved only for nonpregnant patients aged 2-49 years, according to the CDC.



Louise A. Koenig/MDedge News

That said, the spray is especially appropriate for patients who refuse to receive the injected form, so the choice of formulation is at the pediatrician's discretion, according to the AAP release.

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Disruptive behavior on the job linked to depression, burnout

BY RANDY DOTINGA
MDedge News

SAN DIEGO – Hospitals pay a price for bad behavior by staff in the workplace, results of a large multicenter study suggest.

A work culture in which disruptive behavior is tolerated can have consequences. Research on this topic has linked disruptive behavior by staff in the health care setting to increased frequency of medical errors and lower quality of care (Am J Med Qual. 2011 Sep-Oct;26[5]:372-9; J Caring Sci. 2016 Sep 1;5[3]:241-9). This new study, based on a workplace culture survey of 7,923 health care workers and 325 work settings at 16 hospitals in a large West Coast health care system, found higher rates of depression and burnout among staff where disruptive behavior is prevalent, researchers found. The paper was presented by study lead Allison Hadley, MD, of Duke Children's Hospital, Durham, N.C., at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

The investigators developed a novel survey scale for evaluating disruptive behaviors in the health care setting. The objective was to look at the associations between disruptive behavior, teamwork, safety culture, burnout, and depression. Disruptive behaviors included turning backs or hanging up the phone before a conversation is over, bullying or trying to publicly humiliate other staff, making inappropriate comments (with sexual, racial, religious, or ethnic slurs), and physical aggression (such as throwing, hitting, and pushing).

San Francisco internist Alan H. Rosenstein, MD, who studies disruptive behavior in medicine, said in an interview that the findings confirm anecdotal experience of medical staff. "One of the downsides of disruptive behavior is very unsatisfied and unhappy people," he said

The investigators used a t-test analysis to study the strength of the association between disruptive behavior and work culture in health care work settings. They found a statistically significant association between less disruptive behavior and lower levels of burnout and depression among staff (t = 6.4 and t = 4.1, respectively, *P* less than .001) and higher levels of teamwork, safety culture, and work-life balance (t = 10.2, t = 9.5, and t = 5.8, respectively, *P* less than .001). Settings in which disruptive behaviors were more common were more likely to have poor teamwork culture (*P* less than .001) and safety climate (*P* less than .001), and higher rates of depression (*P* less than .001). Settings in which disruptive behaviors were common were more likely to have poor teamwork culture (*P* less than .001) and poor safety climate (*P* less than .001), and higher rates of depression among staff (*P* less than .001).

RANDY DOTINGA/MDEDGE NEWS
Dr. Allison Hadley

Bullying was reported at about 40% of workplaces with low teamwork levels, compared with nearly 20% in those with high teamwork levels.

Physical aggression was reported in nearly 20% of those workplaces with low teamwork levels, compared with 5% in workplaces with high teamwork levels (*P* less than .001).

Researchers also found that disruptive behaviors were least common during day shifts and more common among health care workers who care for both adults and children than among those who care for only adults. "Teamwork, safety culture, and work-life balance were highest in those [hospital] units with the least disruptive behaviors," said Dr. Hadley.

Overall, the highest positive correlation was found between higher levels of teamwork and lower levels of disruptive behavior, Dr. Hadley said. If a hospital department is trying to address one issue to improve disruptive behavior, she'd suggest it "focus on teamwork first. I hope that would have the greatest impact."

No study funding was reported. Dr. Hadley and Dr. Rosenstein reported no relevant disclosures.

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SOURCE: Hadley A et al. Critical Care Congress 2019, Abstract 114.

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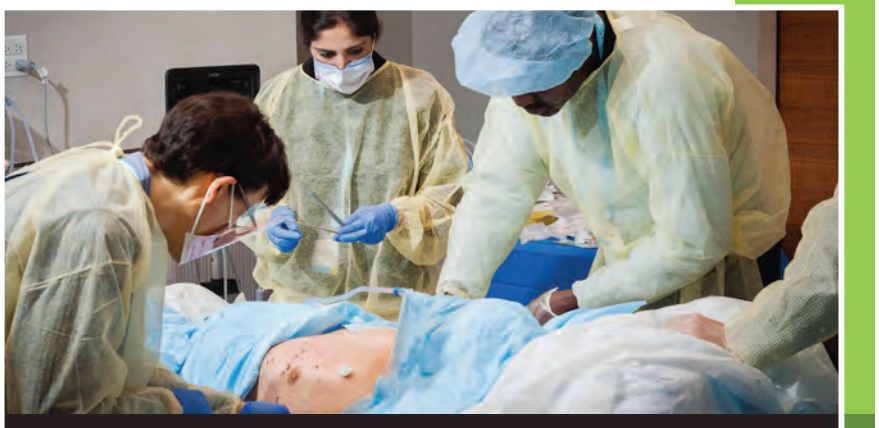

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Updates from your CHEST Board of Regents

BY DAVID A. SCHULMAN, MD, FCCP

In late January, your Board of Regents met for its first face-to-face quarterly meeting under the leadership of new President Clayton Cowl, MD, MS, FCCP. One of the most valuable aspects of serving on the Board is an opportunity to take an overall look at the direction of the organization.

The Board makes a concerted effort not to get too deep into the weeds planning out specific tactics for achieving goals; we have a great many outstanding volunteers serving on dozens of our committees who do an incredible job of making things happen. The Board tries to focus on overall organizational strategy. Are we going in the right direction? Are there opportunities of which we should be taking better advantage? Are there efforts in which we are currently engaged that may not be yielding outcomes as we expected?

To better answer these questions, Dr. Cowl and his team asked all members of the Board of Regents and the Strategic Planning Subcommittee members of the Foundation Board of Trustees, as well as senior CHEST staff, to engage in an environmental scan to take an aggressive look at where we are and where we are headed. The output from our first environmental scan is currently being curated into a list of highest priority items that will be shared with the general membership in the coming months.

A review of our accomplishments over the last 6 months came next. Our new Executive Vice President and Chief Operating Officer, Dr. Robert Musacchio, has superseded all expectations in his first few months in the role. In addition to continuing to push the organization toward the "One CHEST" model by better integrating the Foundation with the College, as well as refining our operating principles in working with industry, Bob is further developing our international reach—exploring collaborations with a number of large international societies and planning meetings abroad this year (CHEST Congress Thailand and CHEST Regional Congress Athens) and into the next (in Italy, with the regional meeting location to be determined).

We are also in the process of recruiting for a new position, Chief Learning Officer, a role that will serve not only to better organize the educational activities of CHEST, but to also serve as a visionary to better imagine what future projects we should be pursuing to be of better service and value to our members.

We took a few moments to recognize the new, incoming Editor in Chief of the journal *CHEST*®; Peter Mazzone, MD, FCCP, will have some huge shoes to fill in taking the editor's chair from Richard Irwin, MD, Master FCCP, who has served the journal in this role for more than a decade.

Under Dr. Irwin's leadership, *CHEST*® journal has been the most-read publication amongst practicing pulmonary specialists; he is also responsible for having launched the journal's social media presence, including both video series that integrated directly with the journal (such as Ultrasound Corner) and podcasts. Richard also spoke beautifully about his passion for patient-centered care as a keynote speaker at CHEST 2018.

Peter has outlined a number of different areas of focus for the journal in the next year, including putting a high priority on improving the reader experience and crafting an even better web and multimedia presence. We look forward to great things from the journal!

Chris Carroll, MD, FCCP, who chairs CHEST's Digital Strategy Task Force, presented to the Board on their progress to date. The goal of this group is to evaluate the user experience for CHEST's content delivery platforms, including the website, apps, and our social media platforms to identify opportunities for improvements that will enable us to better provide our members with on demand, high quality information to improve patient care through a personalized, seamless digital user experience.

The team is being co-led by Nicki Augustyn, Senior Vice President for Marketing, Communications, and Publishing, and Ron Moen, Chief Information Officer. We look forward to further updates on this important project.

As I stated in my opening, many of the good things that CHEST does can only happen with the participation of our great members, and so I want to take the time to recognize the NetWorks and everything that they do for the College. In the past year, under the leadership of Council of NetWorks Chairs Hassan Bencheqroun, MD, FCCP, and David Zielinski, MD, FCCP, the NetWorks produced more than 60% of the content at the 2018 CHEST meeting and are actively working on projects ranging from creating educational videos for public consumption to CHEST guidelines proposals and crafting a donor registry for lung transplantation. Our volunteer leaders are our most valuable resource; if you are not currently engaged in the NetWorks, please consider getting involved this spring during the nomination process!

It remains a privilege for the Board to serve this great organization. If you are interested in hearing more, or getting more engaged, please send me an email at chestphysiciannews@chestnet.org.

Welcoming a new Section Editor for Sleep Strategies

Michelle Cao, DO, FCCP, is a Clinical Associate Professor in the Division of Sleep Medicine and Division of Neuromuscular Medicine, at the Stanford University School of Medicine.

Her clinical expertise is in complex sleep-related respiratory disorders and home mechanical ventilation for chronic respiratory failure syndromes. She oversees the Noninvasive Ventilation Program for the Stanford Neuromuscular Medicine Center. Dr. Cao also holds the position of Vice-Chair for the Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork with CHEST and is a member of the Scientific Presentations and Awards Committee.

CHEST thanks Dr. Chris Lettieri for his time and efforts as the previous Section Editor for Sleep Strategies.

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Thank you to the CHEST 2019 Scientific Program Committee

BY WILLIAM F. KELLY, MD, FCCP

The CHEST 2019 Scientific Program Committee has been working tirelessly to select the best and most clinically relevant sessions for the upcoming meeting. CHEST would like to extend a heartfelt thank you to all who actively participated in grading, curriculum group calls, the live meeting in February, and all the homework in between. We're not done, but your work has been instrumental in making the CHEST Annual Meeting 2019 a success.

Doreen J. Addrizzo-Harris, MD, FCCP
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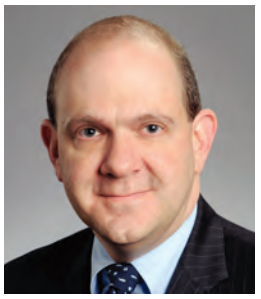

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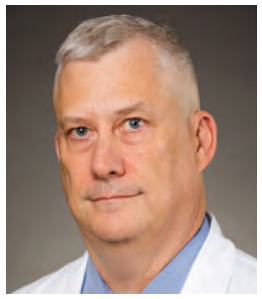

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CHEST® Annual Meeting 2019

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.*

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AstraZeneca

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US-26732 2/19

Fasenra® (benralizumab) Subcutaneous Injection 30 mg

FROM THE START

FASENRA™ (benralizumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE

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

Limitations of use:

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

DOSAGE AND ADMINISTRATION

Recommended Dose

FASENRA is for subcutaneous use only.

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

Preparation and Administration

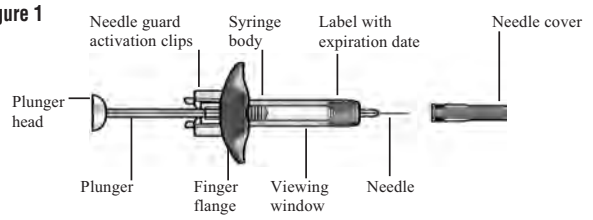
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

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

Instructions for Prefilled Syringe with Needle Safety Guard

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

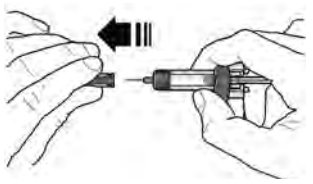
Figure 1



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

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

2



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

3

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

4

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

5

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

6 Discard the used syringe into a sharps container.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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

Acute Asthma Symptoms or Deteriorating Disease

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

Reduction of Corticosteroid Dosage

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

Parasitic (Helminth) Infection

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

28-Week Trial

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

Injection site reactions

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

Immunogenicity

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

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

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

DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

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

Clinical Considerations

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions

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

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*.

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CRITICAL CARE COMMENTARY

Risks of removing the default: Lung protective ventilation IS for everyone

BY KUSUM S. MATHEWS, MD, MPH, MSCR; AND DANIEL HOWELL, MBBS, MSC

Since the landmark ARMA trial, use of low tidal volume ventilation (LTVV) at 6 mL/kg predicted body weight (PBW) has become our gold standard for ventilator management in acute respiratory distress syndrome (ARDS) (Brower RG, et al. *N Engl J Med*. 2000;342[18]:1301). While other studies have suggested that patients without ARDS may also benefit from lower volumes, the recently published Protective Ventilation in Patients Without ARDS (PReVENT) trial found no benefit to using LTVV in non-ARDS patients (Simonis FD, et al. *JAMA*. 2018;320[18]:1872). Does this mean we let physicians set volumes at will? Is tidal volume (Vt) even clinically relevant anymore in the non-ARDS population?

Prior to the PReVENT trial, our practice of LTVV for patients without ARDS was informed primarily by observational data. In 2012, a meta-analysis comparing LTVV with "conventional" Vt (10-12 mL/kg IBW) in non-ARDS patients found that those given LTVV had a lower incidence of acute lung injury and lower overall mortality (Neto AS, et al. *JAMA*. 2012 308[16]:1651). While these were promising findings, there was limited follow-up poststudy onset, and the majority of included studies were based on a surgical population. Additionally, the use of Vt > 10 mL/kg PBW has become uncommon in routine clinical practice. How comparable are those previous studies to today's clinical milieu? When comparing outcomes for ICU patients who were ventilated with low (≤7mL/kg PBW), intermediate (>7, but <10 mL/kg PBW), and high (≥10 mL/kg PBW) Vt, a second meta-analysis found a 28% risk reduction in the development of ARDS or pneumonia with low vs high, but the similar difference was not seen when comparing low vs intermediate groups (Neto AS, et al. *Crit Care Med*. 2015;43[10]:2155). This research suggested that negative outcomes were driven by the excessive Vt.

Slated to be the definitive study on the matter, the PReVENT trial used a multicenter randomized control trial design comparing target Vt of 4 mL/kg with 10 mL/kg PBW, with setting titration primarily based on plateau pressure targets. The headline out of this trial may have been that it was "negative," in that there was no difference between the groups in the primary outcome of ventilator-free days and survival by day 28. However, there are some important limitations to consider before discounting LTVV for everyone. First, half of the trial patients were ventilated with pressure-control ventilation, the actual Vt settings were 7.3 (5.9 – 9.1) for the low group vs 9.1 (7.7 – 10.5) mL/kg PBW for the intermediate group by day 3, statistically significant differences, but perhaps not as striking clinically. Moreover, a secondary analysis of ARDSnet data (Amato MB, et al., *N Engl J Med*. 2015;372[8]:747) also suggests that driving pressure, more so than Vt, may determine outcomes, which, for most patients in the PReVENT trial, remained in the "safe" range of < 15 cm H_2O. Finally, almost two-thirds of patients eligible for PReVENT were not enrolled, and the included cohort had Pao_2/Fio_2 ratios greater than 200 for the 3 days of the study, limiting generalizability, especially for patients with acute hypoxemic respiratory failure.

When approaching the patient who we have determined to not have ARDS (either by clinical diagnosis or suspicion plus a low Pao_2/Fio_2 ratio as defined by PReVENT's protocol), it is important to also consider our accuracy in recognizing ARDS before settling for the use of unregulated Vt. ARDS is often underrecognized, and this delay in diagnosis results in delayed LTVV initiation. Results from the LUNG SAFE study, an international multicenter prospective observational study of over 2,300 ICU patients with ARDS, showed that only 34% of patients were recognized by the clinician to have ARDS at the time they met the Berlin criteria (Bellani G, et al. *JAMA*. 2016;315[8]:788). As ARDS is defined by clinical criteria, it is biologically plausible to think that the pathologic process commences before these criteria are recognized by the clinician.

Dr. Kusum S. Mathews

Dr. Daniel Howell

To investigate the importance of timing of LTVV in ARDS, Needham and colleagues performed a prospective cohort study in patients with ARDS, examining the effect of Vt received over time on the outcome of ICU mortality (Needham DM, et al. *Am J Respir Crit Care Med*. 2015;191[2]:177). They found that every 1 mL/kg increase in Vt setting was associated with a 23% increase in mortality and, indeed, increases in subsequent Vt compared with baseline setting were associated with increasing mortality. One may, therefore, be concerned that if we miss the ARDS diagnosis, the default to higher Vt at the time of intubation may harm our patients. With or without clinician recognition of ARDS, LUNG SAFE revealed that the average Vt for the patients with confirmed ARDS was 7.6 (95% CI 7.5-7.7) mL/kg PBW. While this mean value is well within the range of lung protective ventilation (less than 8 mL/kg PBW), over one-third of patients were exposed to larger Vt. A recently published study by Sjoding and colleagues showed that Vt of >8 mL/kg PBW was used in 40% of the cohort, and continued exposure to 24 total hours of these high Vt values was associated with increased risk of mortality (OR 1.82 (95% CI, 1.20–2.78) (Sjoding MW, et al. *Crit Care Med*. 2019;47[1]:56). All three studies support early administration of lung protective ventilation, considering the high mortality associated with ARDS.

Before consolidating what we know about empiric use of LTVV, we also must highlight the important concerns about LTVV that were investigated in the PReVENT trial. Over-sedation to maintain low Vt, increased delirium, ventilator asynchrony, and possibility of effort-induced lung injury are some of the potential risks associated with LTVV. While there were no differences in the use of sedatives or neuromuscular blocking agents between groups in the PReVENT trial, more delirium was seen in the LTVV group with a $P = .06$, which may be a signal deserving further exploration.

Therefore, now understanding both the upside and downside of LTVV, what's our best approach? While we lack prospective clinical trial data showing benefit of LTVV in patients without ARDS, we do not have conclusive evidence to show its harm. Remembering that even intensivists can fail to recognize ARDS at its onset, default utilization of LTVV, or at least lung protective ventilation of <8 mL/kg PBW, may be the safest approach for all patients. To be clear, this approach would still allow for active physician decision-making to personalize the settings to the individual patient's needs, including the use of higher Vt if needed for patient comfort, effort, and sedation needs. Changing the default settings and implementing friendly reminders about how to manage the ventilator have already been shown to be

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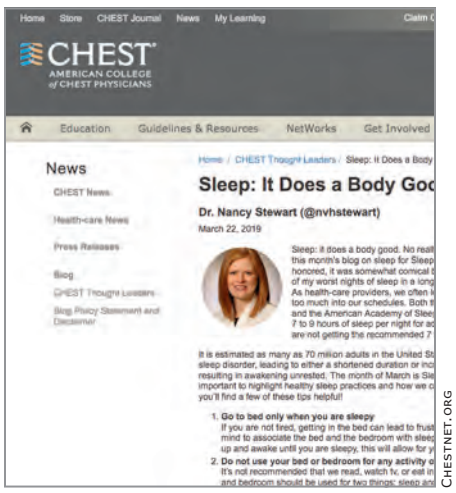
Check out the current CHEST Thought Leaders Blog

Sleep: It Does a Body Good by Dr. Nancy Stewart



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Sleep: it does a body good. No really, it does. When asked to write this month's blog on sleep for Sleep Awareness Month, although honored, it was somewhat comical because the night prior I had one of my worst nights of sleep in a long time, taking care of a sick child. As health-care providers, we often lead stressful lives and pack way too much into our schedules. Both the Centers for Disease Control and Prevention and the American Academy of Sleep Medicine recommend obtaining 7 to 9 hours of sleep per night for adults; unfortunately, many of us are not getting the recommended 7 to 9 hours of sleep.

Find the entire blog at www.chestnet.org/News/Blogs.

Continued from previous page

helpful for the surgical population (O'Reilly-Shah VN, et al. *BMJ Qual Saf*. 2018;27[12]:1008).

We must also consider the process of health-care delivery and the implementation of best practices, after considering the facilitators and barriers to adoption of said practices. Many patients decompensate and require intubation prior to ICU arrival, with prolonged boarding in the ED or medical wards being a common occurrence for many hospitals. As such, we need to consider a ventilation strategy that allows for best practice implementation at a hospital-wide level, appealing to an interprofessional approach to ventilator management, employing physicians outside of critical care medicine, respiratory therapists, and nursing. The PReVENT trial had a nicely constructed protocol with clear instructions on ventilator adjustments with frequent plateau pressure measurements and patient assessments. In the real world setting, especially in a non-ICU setting, ventilator management is not as straightforward. Considering that plateau pressures were only checked in approximately 40% of the patients in LUNG SAFE cohort, active management and attention to driving pressure may be a stretch in many settings.

Until we get 100% sensitive in timely recognition (instantaneous, really) of ARDS pathology augmented by automated diagnostic tools embedded in the medical record and/or incorporate advanced technology in the ventilator management to avoid human error, employing simple defaults to guarantee a protective setting in case of later diagnosis of ARDS seems logical. We can even go further to separate the defaults into LTVV for hypoxemic respiratory failure and lung protective ventilation for everything else, with future development of more algorithms, protocols, and clinical decision support tools for ventilator management. For the time being, a simpler intervention of setting a safer default is a great universal start.

Dr. Mathews and Dr. Howell are with the Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine; Dr. Mathews is also with the Department of Emergency Medicine; Icahn School of Medicine at Mount Sinai, New York, NY.

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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**

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PULMONARY PERSPECTIVES®

Social media for physicians: Strong medicine or snake oil?

BY HASSAN BENCHEQROUN, MD, FCCP

For most of us, social media is a daunting new reality that we are pressured to be part of but that we struggle to fit into our increasingly demanding schedules. My first social media foray as a physician was a Facebook fan page as a hobby rather than a professional presence. Years later, I have learned the incredible benefit that being on social medial in other platforms brought to my profession.

What's social media going to bring to my medical practice?
The days where physicians retreat to the safety of our offices to deliver our care, or to issue carefully structured opinions, or interactions with patients have made way for a more direct interaction. Social media has, indeed, allowed us to share more personal glimpses of our daily struggle to save lives, behind-the-scenes snapshot of ethical struggles in decision making, our difficulties qualifying patients for therapies due to insurance complications, or real-time addressing medical news and combating misinformation. Moreover, when patients self-refer, or are referred to my practice, they look me up online before coming to my office. Online profiles are the new "first impression" of the bedside manner of a physician.

Other personal examples of social media benefits include being informed of new publications, since many journals now have an online presence; being able to interact in real-time with authors; learning from physicians in other countries how they handled issues, such as shortage of critical medications; or earning CME, such as the Twitterchats hosted by CHEST (eg, new biologic agents in difficult to treat asthma, or patient selection in triple therapy for COPD).

Why should I pay attention to social media presence?
The pace by which social media changed the landscape took the medical community by surprise. Patients, third-party websites, and online review agencies (official or not) adopted it well before physicians became comfortable with it. As such, when I decided to google myself online, I was shocked at the level of misinformation about me (as a pulmonologist, I didn't know I had performed sigmoidoscopies, yet that's what my patients learned before they met me). That was an important lesson: *If I don't control the narrative, someone else will*. Consequently, I dedicated a few hours to establish an online presence in order to introduce myself accurately and to be accessible to my patients and colleagues online.

Who decides what's ethical and what's not?
As the lines blurred, our community struggled to define what was appropriate and what was not. Finally, we welcomed with relief the issuance of a Code of Ethics, regarding social media use

Dr. Hassan Bencheqroun

by physicians, from several societies, including the American Medical Association (https://goo.gl/8zX7iM). The principles guiding physicians use of social media include respect for human dignity and rights, honesty and upholding the standards of professionalism, and the duty to safeguard patient confidences and privacy.

Which platform should I use? There are so many.
While any content can be shared on any platform, social media sites have organically differentiated into being more amenable to one content vs the other. Some accounts tend to be more for professional use (ie, Twitter and LinkedIn), and other accounts for personal use (ie, Facebook, Instagram, Snapchat, and Pinterest). CHEST has selected Twitter to host its CME chats regarding preselected topics, post information about an upcoming lecture during the CHEST meeting, etc. New social media sites are now "physician only," such as Sermo, Doximity, QuantiMD, and Doc2Doc. Many of these sites require doctors to submit their credentials to a site gatekeeper, recreating the intimacy of a "physicians' lounge" in an online environment (*J Med Internet Res*. 2014:Feb 11;16[2]:e13). Lastly, *Figure1* is a media sharing app between physicians allowing discussions of de-identified images or cases, recreating the "curbside" consult concept online.

I heard about hashtags. What are they?
Hashtags are simply clickable topic titles (#COPD #Sepsis # Education, etc) that can be added to a post, in order to widen its reach. For instance, if I am interested in sepsis, I can click on the hashtag #Sepsis, and it would bring up all the posts on any Twitter account that added that hashtag. It's a filter that takes me to that topic of interest. I can then click on the button "Like" on the message or the account itself where the post was found. The "Like" is similar to a bookmark for that account on my own Twitter. In the future, all the posts from that account would be available to me.

What are influencers or thought leaders?
Anyone who "liked" my account is now "following" me. The number of followers has become a measure of popularity of anyone on social media. If it reaches a high level, then the person with the account is dubbed an "influencer." Social media "influencers" are individuals whose opinion is followed by hundreds of thousands. Influencers may even be rewarded for harnessing their reach to make money off advertising. One can easily see how it is powerful for a physician to become an influencer or a "thought leader," not to make money but to expand their reach on social media to spread the correct information about diets, drugs, e-cigarettes, and vaccinations, to name a few.

Can social media get me in trouble?
In 2012, a survey of the state medical boards published by *JAMA* (2012;307[11]:1141) revealed that approximately 30% of state medical boards reported complaints of "online violations of patient confidentiality." More than 10% stated they had encountered a case of an "online depiction of intoxication."

Another study a year earlier revealed that 13% of physicians reported they have discussed individual, though anonymized, cases with other physicians in public online forums (http://www.quantiamd.com/qqcp/DoctorsPatientSocialMedia.pdf).

Even if posted anonymously, or on a "personal" rather than professional social media site, various investigative methods may potentially be used to directly link information to a specific person or incident. The most current case law dictates that such information is "discoverable." In fact, Facebook's policy for the use of data informs users that, "*we may access, preserve, and share your information in response to a legal request" both within and outside of U.S. jurisdiction*".

What kind of trouble could I be exposed to?
Poor quality of information, damage to our professional image, breaches of patient's privacy, violation of patient-physician boundary, license revoking by state boards, and erroneous medical advice given in the absence of examining a patient, are all potential pitfalls for physicians in the careless use of social media.

How can I minimize my legal risk when interacting online?
It has been suggested that a legally sound approach in response to requests for online medical advice would be to send a standard response form that:

- informs the inquirer that the health-care provider does not answer online questions;
- supplies offline contact information so that an appointment can be made, if desired; and
- identifies a source for emergency services if the

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inquirer cannot wait for an appointment.

In circumstances where a patient–physician relationship already exists, informed consent should be obtained, which should include a careful explanation regarding the risks of online communication, expected response times, and the handling of emergencies, then documented in the patient's chart (*PT*. 2014 Jul;39[7]:491,520).

In summary

Social media, much like any area of medicine one is interested in, can be daunting and exciting but fraught with potential difficulties. I liken its adoption in our daily practice to any other decision or interest, including being in a private or academic setting, adopting procedural medicine or sticking to diagnostic consultations, or participating in research. In the end, it's an individual expression of our desire to practice medicine. However, verifying information already existing online about us is of paramount importance. *If I don't tell my story, someone else will, and they may not be as truthful.*

Dr. Bencheqroun is Assistant Professor, University of California Riverside School of Medicine, Pulmonary/Critical Care Faculty Program Coordinator & Research Mentor - Internal Medicine Residency Program Desert Regional Medical Center, Palm Springs CA; and Immediate Past Chair of the CHEST Council of NetWorks.

On your mark, get set, *GO!*

The NetWorks Challenge is now underway

We are so excited to once again host the NetWorks Challenge. During the next 3 months, you have the opportunity to be a Champion and make a donation to the CHEST Foundation. Every time you contribute, you can designate a NetWork of your choice to benefit from your gift. Each NetWork is eligible to receive travel grants to CHEST 2019 based on the amount raised.

Last year, we more than doubled the number of early career clinician travel grants to attend CHEST 2018. This year, we want to raise the bar again. Don't delay, make a donation today by visiting Chestfoundation.org/donate and be a Champion for your NetWork!

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**.

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.

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.

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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 participation rate, 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!

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- Diagnosing Severe Asthma: Not as Easy as it Sounds
- Bronchial Thermoplasty: A Viable Option for Severe Asthma

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CHEST NETWORKS

Black lung. Choosing the right words. Low-tidal volume. Recent key OSA articles.

Occupational and Environmental Health

Black lung disease in the 21st century

Inhalation and deposition of coal dust particles cause a range of lung injury from coal workers' pneumoconiosis (CWP) to dust-related diffuse fibrosis to COPD. Despite workplace standards and improved environmental controls to limit dust exposure within coal mines, incidence of "black lung disease" in the United States has increased since the turn of the century (Antao VC, et al. *Occup Environ Med*. 2005;62[10]:670).

Coal miners working in the Appalachian Mountains have been particularly vulnerable to developing rapidly progressive and severe pneumoconiosis. In 2018, three black lung clinics in central Appalachia uncovered the largest cluster of progressive massive fibrosis (PMF) ever reported (Blackley DJ, et al. *JAMA*. 2018;319[5]:500).

An investigation by National Public Radio (NPR) and the Public Broadcasting Service (PBS) program Frontline identified more than 2,000 Appalachian coal miners suffering with PMF from 2011 to 2016, while only 99 cases of PMF were identified by the current federal monitoring program during the same period (https://goo.gl/ZJXp1W).

Dr. Harris

Dr. Ahasic

Only about one-third of coal miners may participate in screening for black lung disease, and lack of participation could result from barriers such as fear of retaliation from employers (Siddons A. CQ-Roll Call, Inc. March 1, 2019; https://goo.gl/5mfVFv).

Ongoing research is studying factors leading to the resurgence in CWP. Increasing silica content in coal dust is a likely culprit that has escaped mine safety regulations. Given the rising incidence and the increasing morbidity and mortality of black lung disease, there is a need to educate and engage pulmonologists and others to improve surveillance and early recognition of the spectrum of coal-dust-related lung diseases to decrease morbidity and mortality among this vulnerable occupational group.

Drew Harris, MD
Amy Ahasic, MD, MPH, FCCP
Steering Committee Members

Palliative and End-of-Life Care

Importance of language and word choice when discussing cardiopulmonary resuscitation (CPR)

Words matter. Whether spoken or written, the words we choose when communicating with each other are fundamentally important, both by intention of the originator and the understanding of the audience, whether or not the meaning is imparted faithfully.

In medicine, we identify patients with their illness, "the septic patient," or category, "the terminal patient" or "the DNR patient" (Altillio, et al. *AAHPM Quarterly*. 2013;14-18).

We escape responsibility for adequate communication by adopting a language filled with anatomic and pharmaceutical references where we blame patients for their disease process, eg, "the patient failed extubation" or "the patient is noncompliant." We tend to resort to medical jargon or terror language in order to achieve the desired outcome. Never is this more evident than when discussing code status. In the ICU, when one hopes to "get the DNR," it is not uncommon to hear the phrase, "If your heart stops, we would have to break all of your ribs, and that would be torture."

Dr. Moses

Dr. Kelemen

While the data are clear on harm-

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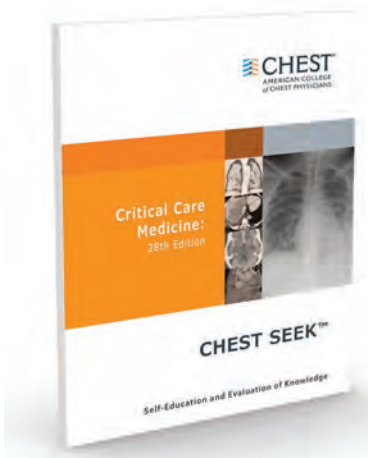

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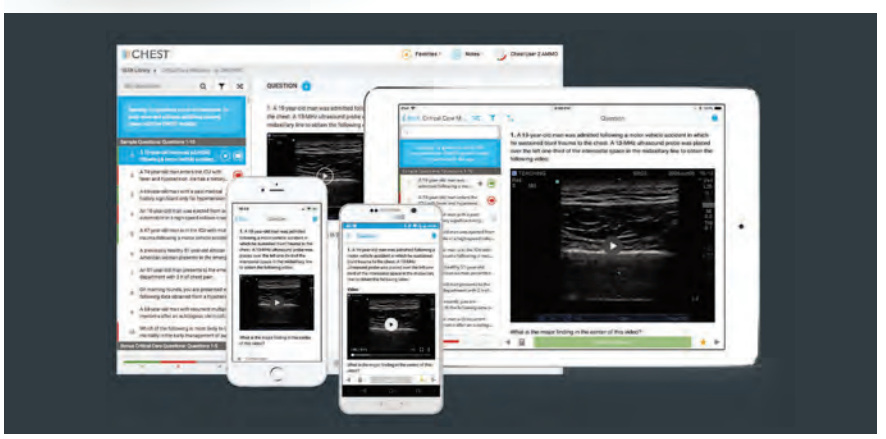

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This month in the journal *CHEST*®

Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Giants in Chest Medicine

David C. Zavala, MD, FCCP

Original Research

Accuracy of Algorithms to Identify Pulmonary Arterial Hypertension in Administrative Data: A Systematic Review.
By K. R. Gillmeyer, et al.

Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory.
By M. L. Salisbury, et al.

The Effects of Long-term CPAP on Weight Change in Patients With Comorbid OSA and Cardiovascular Disease: Data From the SAVE Trial.
By Q. Ou, et al, on behalf of the SAVE investigators.

Five things to do near the convention center in NOLA

While CHEST 2019 will have your days busy, don't forget to find time to explore entertaining, cultural, and historic places around New Orleans. Grab your friends and colleagues for some fun, and try out a few of these places!

1. House of Blues New Orleans
If you're already heading to the city known for jazz and blues, there's no better place to experience that than the House of Blues New Orleans. Enjoy live music and great food under one roof. Be sure to check the House of Blues website as the annual meeting draws nearer to see which concerts and events will be happening in October.

2. Audubon Aquarium of the Americas
Located just north of the convention center, head over to the Audubon Aquarium of the Americas. During the fall and winter months, the aquarium has less traffic, which allows you to take in all the animals and exhibits at your own pace. See exhibits like the Great Maya Reef, a walk-through tunnel into a submerged Maya city of the Yucatan peninsula; the penguins, sea otters, or the sharks and rays in the 400,000-gallon Gulf of Mexico Exhibit.


Ed Bierman /Creative Commons
Ogden Museum of Southern Art

3. Ogden Museum of Southern Art
Less than 5 minutes from the convention center, the Ogden Museum of Southern Art holds the largest and most comprehensive collection of southern art, including visual art, music, literature, and culinary heritage. If you're in the city before or after the annual meeting, catch a guided tour on a Thursday afternoon. Tours are free with admission into the museum. Check their website for museum hours.

4. Escape My Room
Who doesn't love a good escape room? At Escape My Room, look for clues and hints to help the DeLaporte family as you're transported through history into the DeLaporte Family Museum. Bring your family or team in a group of up to eight, depending on the room, and see if you can solve the mystery.

5. A walking tour of the Garden District
Take a cable car a few stops to the Garden District, a historic neighborhood in New Orleans. This picturesque neighborhood showcases plantation-style mansions, streets separated by stretches of green parks, and the historic Lafayette Cemetery No. 1 and cable car line that runs along St. Charles Avenue. There are guided tours available, but you can also choose to take a self-tour of the area.

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ful effects of CPR, and its general lack of success for people with a serious illness (Dunham, et al. *Eur Radiol*. 2018;28[10]:4122), it is unnecessary to use threatening language in our communication.

Compassionate care begins and ends with effective communication. The Palliative and End of Life Care NetWork supports making better word choices. We encourage framing end-of-life care around what will continue to work to help support the patient and not doing things that we know do not work.

"We will do everything to help manage his/her breathing and heart rate, and when his/her heart stops, we will allow him/her to die naturally" (Curtis, et al. *Intensive Care Med.* 2014;40:606).

Benjamin Moses, MD
Anne Kelemen, LICSW
Steering Committee Members

Respiratory Care
Low-tidal volume ventilation

Mechanical ventilation in postoperative (post-op) patients is essential in care because it can determine the patient's overall outcome, especially in post-op cardiovascular surgery patients. The risks of hemodynamic instability and consideration of total body organ function make choosing the correct strategy of mechanical ventilation vital (Ball, et al. *Crit Care*. 2016;22[4]:386).

The current standard of practice for mechanically ventilated patients is to use low-tidal volume (LTV) ventilation, meaning administering 6-7 mL/kg of ideal body weight (Hoegl, et al. *Anesthesiology*. 2016;29[4]:94).


Dr. Markos

The benefits of LTV ventilation include significantly decreased risk in lung injury, decreased risk of developing ARDS, and lessening of hemodynamic compromise (Hoegl, et al. *Anesthesiology*. 2016;29[4]:94; Stephens, et al. *Crit Care Med*. 2015;43:1477).

Also, due to its high efficacy in terms of cost-effective care, such as shorter ICU stays and less number of days supported by mechanical ventilation, many hospitals have incorporated LTV strategy into the care of almost all post-op patients (Stephens, et al. *Crit Care Med*. 2015;43:1477).

However, no randomized controlled trials have been conducted in post-op cardiovascular patients undergoing mechanical ventilation to determine if LTV ventilation (6-7 mL/kg) has superior efficacy over higher levels of ventilation (8-10 mL/kg). This patient population tends to have normal lung function and, therefore, a LTV strategy could possibly be too conservative, whereas larger tidal volumes may be more comfortable and provide better ventilation considering the increased dead space in post-op cardiovascular patients.

In order to address this gap in the literature, it is essential to determine if significant differences exist in patient mortality, ventilator days, hospital stay, and incidence of pulmonary complications for this population undergoing ventilation volumes of approximately 6 mL/kg or 8 mL/kg of ideal body weight.

Bethlehem Markos
Steering Committee
Fellow-in-Training

Sleep Medicine
In case you missed it: Recent findings in obstructive sleep apnea

On behalf of the Sleep Medicine NetWork, I would like to highlight a few key articles related to OSA:

A potential drug combo to treat OSA (Taranto-Montemurro, et al. *Am J Respir Crit Care Med.* Articles in Press. Published on 05-November-2018 as 10.1164/rccm.201808-1493OC) The apnea-hypopnea index (AHI) decreased by over 20 events/hour in a small group of patients receiving atomoxetine and oxybutynin, presumably via increased activity of the upper airway dilator muscles.

CPAP may reduce hospitalizations (Truong, et al. *J Clin Sleep Med*. 2018;14[2]:183) Patients nonadherent to CPAP had greater all-cause 30-day readmission rates over an 8-year period after adjusting for comorbidities, suggesting the potential of CPAP to prevent recurrent hospitalizations.


Dr. Tobias

Patients getting in-lab sleep testing are increasingly complex (Colaco, et al. *J Clin Sleep Med*. 2018;14[4]:631) Patients undergoing PSG as opposed to home testing have more medical comorbidities than in the past, with implications for how labs are staffed and what monitoring is available.

OSA severity predicts amyloid burden (Sharma. *Am J Respir Crit Care Med*. 2018;197[7]:933) This study highlights a potential pathway in which OSA impacts amyloid deposition and, thereby, vulnerability to developing Alzheimer disease.

A drug for residual sleepiness in OSA (Schweitzer, et al. *Am J Respir Crit Care Med* Articles in Press. Published on 06-December-2018 as 10.1164/rccm.201806-1100OC) For patients with OSA whose sleepiness persisted despite PAP adherence, this 12-week randomized trial showed dose-dependent improvements in wakefulness with use of solriamfetol, a dopamine/norepinephrine reuptake inhibitor.

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Steering Committee Member

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