The Food and Drug Administration once again has upped the ante in its war on youth smoking and vaping.

“Today, I’m pursuing actions aimed at addressing the disturbing trend of youth nicotine use and continuing to advance the historic declines we’ve achieved in recent years in the rates of combustible cigarette use among kids,” FDA Commissioner Scott Gottlieb, MD, said in a statement.

First and foremost, the FDA wants to reduce the lure of e-cigarettes by limiting the variety of flavored products for sale in retail outlets. Under the proposal unveiled Nov. 15, only electronic nicotine delivery systems (ENDS) that are unflavored or have tobacco, mint, or menthol flavors would be widely available. Flavored products – think cherry, cotton candy, and mango – would be sold in age-restricted environments, such as stand-alone tobacco retailers like vape shops. The FDA also seeks more stringent enforcement of age verification on ENDS products sold online.

The proposal also would reexamine regulations governing flavored cigars, with the possible aim of banning them.

“These efforts to address flavors and protect youth would dramatically impact the ability of next-generation products to attract and entice kids in the years ahead,” said FDA Commissioner Scott Gottlieb, MD.

A group of internists is suing the American Board of Internal Medicine over its maintenance of certification (MOC) process, alleging that the board is monopolizing the MOC market.

The lawsuit, filed Dec. 6, 2018, in Pennsylvania district court, claims that ABIM is charging inflated monopoly prices for maintaining certification, that the organization is forcing physicians to purchase MOC, and that ABIM is inducing employers and others to require ABIM certification. The four plaintiff-physicians are asking a judge to find ABIM in violation of federal antitrust law and to bar the board from continuing its MOC process. The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications. The plaintiffs seek damages and injunctive relief, plus lawsuit and attorney costs arising from ABIM’s alleged antitrust violations.

In a statement, ABIM expressed disappointment at the lawsuit and said the organization will vigorously defend itself, adding that doing so will “consume resources far better dedicated...
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.
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.

DEMONSTRATED EFFICACY
In clinical trials, Esbriet preserved more lung function by delaying disease progression for patients with IPF.1,2

ESTABLISHED SAFETY AND TOLERABILITY
The safety and tolerability of Esbriet were evaluated based on 1247 patients in 3 randomized, controlled trials.3

COMMITTED TO PATIENTS
Genentech offers a breadth of patient support and assistance services to help your patients with IPF.4

WORLDWIDE PATIENT EXPERIENCE
More than 37,000 patients have taken pirfenidone worldwide.5

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).1,2 In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had percent predicted forced vital capacity (%FVC) between 50%–90% and percent predicted diffusing capacity of lung for carbon monoxide (%DLco) 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 %DLco ≥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

Mild (CLcr, 50–80 mL/min), moderate (CLcr, 30–50 mL/min), or severe (CLcr, <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.


Learn more about Esbriet and how to access medication at EsbrietHCP.com
Teenage use of vaping devices jumped significantly in the past year, with 37% of 12th-grade students reporting any vaping in 2018, compared with 28% in 2017, data announced Dec. 17 from the 2018 Monitoring the Future survey show. In particular, nicotine-vaping use in the 30 days prior to the survey nearly doubled among high school seniors, from approximately 11% in 2017 to 21% in 2018. Nicotine vaping also increased by 7.9% (from 8.2% to 16.1%) among 10th graders and by 2.6% (from 3.5% to 6.1%) among 8th graders, according to the survey results.

Vaping involves using a device such as an e-cigarette to inhale a heated aerosol product that usually contains nicotine but can be used to

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ESBRIET 2403 mg/day (N = 623)</th>
<th>Placebo (N = 624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Rash</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>24%</td>
<td>15%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>27%</td>
<td>25%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>19%</td>
</tr>
<tr>
<td>Headache</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*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 (6% vs. 3%), abdominal pain (6% vs. 5%), and 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

- **Infections and Infestations**
  - Hepatitis
  - Infection
  - Hepatitis

- **Metabolism and Nutrition Disorders**
  - Deficiency

**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

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**BRIEF SUMMARY**

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

1 INDICATIONS AND USAGE

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

2 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 there 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 reported to ESBRIET have been reported.

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 in 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].

5.3 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 18.3% of patients in the 2403 mg/day group, as compared to 8.8% of patients in the placebo group. 22.2% 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, 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 (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 white (95%). The mean duration of exposure to ESBRIET was 82 weeks (range: 2 to 118 weeks) in these 3 trials.

At the recommended dosage of 2403 mg/day, 14.8% 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.
administer other types of drugs, said Nora D. Volkow, MD, director of the National Institute on Drug Abuse at the National Institutes of Health, in a press conference announcing the findings.

The increased prevalence of nicotine vaping in 10th and 12th graders is the largest annual increase in use of any substance recorded by Monitoring the Future, said Richard A. Miech, PhD, MPH, of the Institute for Social Research at the University of Michigan, Ann Arbor, and the principal survey investigator. "Something about this delivery device of vaping seems to really appeal to kids," he said. The flavorings, concealability of the devices (which can be about the size of a flash drive), and ease of use seem to be contributing to the popularity of vaping, Dr. Miech added.

In addition, marijuana vaping increased significantly across all three grade levels in 2018 from 2017. Within 30 days of the survey, marijuana vaping increased from 4.9% to 7.5% in 12th graders, from 4.3% to 7.0% in 10th graders, and from 1.6% to 2.6% in 8th graders.

A take-home message for clinicians is the need to emphasize to teens that "vaping is not innocuous and not harmless," said Dr. Miech in a question-and-answer session. Of note, data from multiple studies show that children who vape are about five times more likely to smoke cigarettes, he said.

The vaping devices are manufactured to deliver drugs into the lungs and ultimately high concentrations into the brain – which suggests the use of vaping devices to deliver other types of drugs might increase in the future, Dr. Volkow added.

Use of most other substances, including inhalants, heroin, cocaine, and ecstasy; overall marijuana use, alcohol use, and extreme binge drinking remained stable, the researchers said. Cigarette smoking declined slightly among 12th graders but did not change significantly among 8th or 10th graders. Use of prescription opioids and tranquilizers declined in 2018 across all age groups.

"Vaping is reversing hard-fought declines in the number of adolescents who use nicotine," Dr. Miech said in the news release announcing the results. "These results suggest that vaping is leading youth into nicotine use and nicotine addiction, not away from it."

The data on vaping and nicotine use among American teens were published in a letter (N Engl J Med. 2018 Dec 17: doi: 10.1056/NEJMc1814130) – with a warning. "These results indicate that the policies in place as of the 2017-2018 school year were not sufficient to stop the spread of nicotine vaping among adolescents," wrote the authors, led by Dr. Miech. "The rapid entry of new vaping devices on the market ... will require continual updates and modification strategies to keep adolescents from vaping and its associated negative health effects."

The survey is funded by a government grant to the University of Michigan, Ann Arbor, from the NIH's NIDA.
American kids to access tobacco products that we know are both appealing and addicting," Dr. Gottlieb said in a statement.

He concluded, "This policy framework reflects a redoubling of the FDAs efforts to protect kids from all nicotine-containing products."

In a move that seems to be aimed at youth-oriented products like Juul, the FDA will be seeking to remove from the market any ENDS product that is marketed specifically to young people.

Finally, the FDA intends to pursue regulation that would ban menthol from combustible tobacco products.

"I believe these menthol-flavored products represent one of the most common and pernicious routes by which kids initiate on combustible cigarettes," Alex M. Azar II, secretary of the Department of Health & Human Services, said in a statement supporting the FDAs efforts.

He added, "Our obligation at HHS is always to the public health, and we believe FDAs goals strike the right public health balance in addressing the multifaceted challenge we have before us today."

The FDA proposals were published as part of an advance notice of proposed rulemaking in the Federal Register.

FDA warns public about undeclared drugs in e-liquids

BY LUCAS FRANKI
MDedge News

The Food and Drug Administration has issued an alert regarding two e-liquids sold by HelloCig Electronic Technology that contain undeclared prescription drugs.

E-liquid is the flavored mixture used in electronic cigarettes. In a laboratory analysis, the FDA found that "E-Calis HelloCig E-Liquid" contained both sildenafil and tadalafil, and that "E-Rimonabant HelloCig E-Liquid" contained sildenafil.

Sildenafil and tadalafil can interact with nitrates found in some prescription drugs and can cause a dangerous lowering of blood pressure. Conditions commonly treated with nitrates include diabetes, high blood pressure, high cholesterol, or heart disease.

"FDA urges consumers to stop using these products and to contact their health care professional with any concerns associated with their use," the agency stated in a press release.
to continuous improvement of its programs.”

ABIM declined to answer questions addressing specific accusations from the lawsuit. However, in an interview, ABIM President Richard Baron, MD, said that “ABIM board-certified physicians have taken the initiative to distinguish themselves. This is a credential that physicians earn. We offer certified physicians the opportunity to demonstrate to the medical community, their peers, and the public that they are current and have special expertise.”

At press time, ABIM has not yet filed a formal response to the lawsuit, which was due by Jan. 6. From there, discovery and evidence gathering in the case will begin.

Katherine Murray Leisure, MD, an infectious disease specialist based in Plymouth, Mass., is one of the plaintiffs. While she said that she could not comment specifically on the lawsuit, she has written publicly about her ABIM concerns in the past.

In a 2015 letter to Dr. Baron and posted on an anti-MOC website, Dr. Murray Leisure outlined a litany of complaints against ABIM’s MOC process and called on the U.S. Congress to investigate ABIM’s financial, legal, and ethical conduct.

“The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications. The plaintiffs seek damages and injunctive relief, plus lawsuit and attorney costs.”

“[The American Board of Medical Specialties] and ABIM collected more than $10,000 in fees and lost practice hours every decade from each [diplomate] doing MOC,” Dr. Murray Leisure wrote. “MOC took weeks away from our offices, clinics, patients, families, specialty societies, and individual research. ABMS MOC removed hundreds, perhaps thousands … of America’s best, once board-certified physicians from full hospital careers and earnings whenever … [diplomates] did not complete these high-stakes MOC programs. … The righteous and fast solution to such moral, ethical, scientific, and constitutional problems is to end MOC now.”

Plaintiffs Glen Dela Cruz Manalo, MD; Alexa Joshua, MD; and Gerard Kenney, MD, did not return messages seeking comment. When contacted, attorneys for the plaintiffs declined to comment.

The doctors’ 32-page lawsuit characterizes ABIM as an organization motivated by money that has made its MOC process increasingly more burdensome for physicians over the years without evidence that MOC has any beneficial impact on doctors, patients, or the public. Complying with ABIM’s MOC costs internists an average of $23,607 in financial cost and time lost over 10 years, and costs up to $40,495 for some specialists, according to the suit.

The physicians allege that ABIM controls in excess of 95% of the market for MOC of internists, in violation of federal antitrust laws, and that the organization has unlawfully obtained and maintained monopoly power for MOC services.

The board’s illegal tying of its initial certification to its MOC results in burdensome conditions, including “raising the cost of the practice of medicine, constraining the supply of interns thereby harming competition, decreasing the supply of certified internists, and increasing the cost of medical services to patients and consumers,” the suit claims.

The legal challenge details how MOC has personally and professionally impacted each of the four plaintiffs. Dr. Manalo, a gastroenterologist, lost his privileges at St. Vincent Healthcare in Billings, Mont., and was subsequently terminated after he declined to maintain his ABIM certification as a gastroenterologist. In a letter to ABIM, Dr. Manalo wrote that it was “unfair and outright discriminatory that practitioners certified on or after 1990 are the only ones required to certify,” according to the lawsuit. Dr. Manalo later took a position as staff gastroenterologist at Jonathan M. Wainwright Memorial Veterans Affairs Medical Center in Walla Walla, Wash., at a substantially reduced salary. He became unemployed in 2017.

Dr. Murray Leisure obtained an initial and lifelong board certification in internal medicine from ABIM in 1984 and an infectious disease certification in 1990. ABIM terminated Dr. Murray Leisure’s infectious diseases certification after she failed her MOC examination in 2009, which led to lost privileges at Jordan Hospital in Plymouth, Mass. The loss caused significant damage to Dr. Murray Leisure, including lost income, tarnished reputation, and the lost opportunity to help patients, according to the lawsuit. Jordan Hospital restored her privileges after Dr. Murray Leisure passed her MOC examination in 2012.

Dr. Kenney lost a job opportunity with Mount Nittany Physicians Group in State College, Pa., after he declined to renew his ABIM certification in gastroenterology. He is currently a physician with the University of Pittsburgh Medical Center in Seneca, Pa.

That the ABIM website lists him as “not certified,” is misleading, and makes it appear that his initial certifications were revoked due to failure to pass a MOC examination or misconduct, rather than because the certifications lapsed, according to the suit. The description makes Dr. Kenney appear less qualified to patients, hospitals, insurance companies, medical corporations, other employers, and others, he claims.

Dr. Joshua could not renew her consulting and admitting privileges at Detroit Medical Center after she failed an MOC examination in 2014 and became uncertified in internal medicine, according to the suit. In addition, Blue Cross Blue Shield informed Dr. Joshua it would no longer cover her because it required ABIM certification for coverage. She unsuccessfully appealed based on her certification with the National Board of Physicians and Surgeons. As a result of her certification termination, Dr. Joshua can only practice outpatient medicine at Detroit Medical Center.

In an interview, Dr. Baron emphasized the number of modifications made to its MOC process in recent years after responding to physician concerns. This includes an overhaul of the organization’s governance structure to include more than 200 practicing physicians and opening new avenues for physicians to engage in the creation of assessment content that more closely reflects what they see in practice, he said. In addition, ABIM now surveys all specialists to contribute to the exam blueprint review and the creation of the new Item Writing Task Force.

“We take all suggestions from physicians seriously, and have used it to launch many new initiatives including the Knowledge Check-In, a new Physician Portal, partnerships to give physicians dual credit for CME and MOC, and exploration of alternative assessment models with medical societies,” he said.

Dr. Baron acknowledged past criticism of the MOC process, but said he is proud of the work ABIM has done to address physician concerns about the choice, relevance, and convenience of its MOC program.
Non-TB mycobacteria infections rising in COPD patients

**BY JENNIE SMITH**

*MDedge News*

Veterans with chronic obstructive pulmonary disease (COPD) have seen a sharp increase since 2012 in rates of non-TB mycobacteria infections, which carry a significantly higher risk of death in COPD patients, according to findings from a nationwide study.

For their research, published in Frontiers of Medicine, Fahim Pyarali, MD, and colleagues at the University of Miami, reviewed data from Veterans Affairs hospitals to identify non-TB mycobacteria (NTM) infections among more than 2 million COPD patients seen between 2000 and 2015. Incidence of NTM infections was 34.2 per 100,000 COPD patients in 2001, a rate that remained steady until 2012, when it began climbing sharply through 2015 to reach 70.3 per 100,000 (P = .035). Dr. Pyarali and colleagues also noted that, during the study period, prevalence of NTM climbed from 93.1 infections per 100,000 population in 2001 to 277.6 per 100,000 in 2015.

Hotspots for NTM infections included Puerto Rico, which had the highest prevalence seen in the study at 370 infections per 100,000 COPD population; Florida, with 351 per 100,000; and Washington, D.C., with 309 per 100,000. Additional hotspots were identified around Lake Michigan, in coastal Louisiana, and in parts of the Southwest.

Dr. Pyarali and colleagues noted that the geographical concentration of cases near oceans and lakes was "supported by previous findings that warmer temperatures, lower dissolved oxygen, and lower pH in the soils and waters provide a major environmental source for NTM organisms"; however, the study is the first to identify Puerto Rico as having exceptionally high prevalence. The reasons for this should be extensively investigated, the investigators argued.

The mortality risk was 43% higher among NTM-infected patients than in COPD patients without an NTM diagnosis (95% confidence interval, 1.31-1.58; P less than .001), independent of other comorbidities.

Though rates of NTM infection were seen rising steeply in men and women alike, Dr. Pyarali and colleagues noted as a limitation of their study its use of an overwhelmingly male population, writing that this may obscure "the true reach of NTM disease and mortality" in the general population.

The average age of NTM diagnosis remained steady throughout the study period, suggesting that rising incidence is not attributable to earlier diagnosis.

Dr. Pyarali and colleagues reported no outside sources of funding or financial conflicts of interest.


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**Biomarkers predict asthma/COPD risk in 9/11 first responders**

**BY HEIDI SPLETE**

*MDedge News*

**FROM THE JOURNAL CHEST®** Elevated eosinophil levels and interleukin-4 (IL-4) levels were significantly associated with an increased risk of overlapping asthma and chronic obstructive pulmonary disease (COPD) in firefighters exposed to toxins at the World Trade Center on Sept. 11, 2001.

Patients with asthma/COPD overlap experience decreased quality of life and increased mortality, compared with patients who have either isolated COPD or isolated asthma, and longitudinal data on risk factors for the overlapping condition are lacking, wrote Ankura Singh, MPH, of Albert Einstein College of Medicine, New York, and colleagues.

In a study published in CHEST, the researchers reviewed data from 2,137 firefighters exposed to toxins at the World Trade Center on 9/11. The study participants underwent a bronchodilator pulmonary function test between Sept. 9, 2001, and Sept. 10, 2017, and at least three routine monitoring pulmonary function tests between these two dates.

In a multivariate analysis, eosinophil concentration of at least 300 cells/mcL was a significant predictor of asthma/COPD overlap. Serum IL-4 levels also were significant predictors of asthma/COPD overlap (hazard ratio, 1.51).

In addition, a greater concentration of IL-21 was associated with both isolated asthma and isolated COPD, but not with the overlap. The study results were strengthened by the availability of pre-exposure medical data for the firefighters and the close follow-up, although limitations included the mostly white male population and a limited definition of asthma, the researchers noted.

However, the findings suggest that “high eosinophil concentrations, uniquely associated with asthma/COPD overlap in this population, may reflect biological pathways that predispose one to exaggerated inflammation and/or poor counterregulatory responses to inflammation, leading to reversible and fixed airflow obstruction,” they wrote. Consequently, early interventions targeting specific inflammatory pathways may improve lung function outcomes.

The study was supported in part by the National Institute of Occupational Safety and Health and the National Institutes of Health.

**SOURCE:** Singh A et al. CHEST. 2018 Dec;154;1301-10.
New HHS fitness guidelines break new ground

BY BRUCE JANCIN
MEdge News

CHICAGO – The newly released comprehensive second edition of the federal physical activity guidelines have a lofty goal.

“Our overarching vision is to transform the current sick care system into a health promoting system,” Adm. Brett P. Giroir, MD, declared in introducing the recommendations at the American Heart Association scientific sessions.

“Physical activity is one of the most effective preventive health interventions available, and we need more emphasis on prevention as we transition to a value-based reimbursement structure that rewards better health maintenance and avoids chronic conditions,” added Adm. Giroir, assistant secretary for health at the U.S. Department of Health & Human Services.

Although the agency opted to unveil the new guidelines before an audience of cardiologists at the AHA scientific sessions, the report includes sections relevant for a wide range of medical specialists, including primary care physicians, pediatricians, psychiatrists, neurologists, endocrinologists, and geriatricians.

Before launching into a description of what’s new in the second edition, Adm. Giroir set the stage with blunt talk about the nation’s poor state of physical fitness.

"Inactivity causes 10% of premature mortality in the United States. That means if we can just get 25% of inactive people to be active and meet the recommendations, almost 75,000 deaths per year would be prevented in the United States. And on an even larger scale worldwide, if 25% of those same people who are inactive started moving and met the guidelines, more than 1.3 million deaths would be prevented,” according to Adm. Giroir.

At present, only 26% of men, 19% of women, and 20% of teenagers meet the physical activity recommendations.

Failure to meet the federal aerobic physical activity recommendations accounts for an estimated nearly $117 billion in annual health care costs. And it poses a national security threat, too: Nearly one-third of all 17- to 24-year-olds are disqualified from military service because of obesity. Even more eye-opening, he continued, is that fully 71% of all 17- to 24-year-olds are ineligible for military service because of obesity.

lack of physical fitness, lack of education, or substance use.

The actual recommendations contained in the second edition of the Physical Activity Guidelines for Americans remain unchanged from those in the first, issued a decade earlier. That is, in order to gain substantial health benefits, adults and adolescents should engage in at least 150-300 min/week of moderate intensity aerobic physical activity or 75-150 min/week of vigorous intensity aerobic activity. Plus they should do muscle-strengthening exercises such as weight lifting or push-ups at moderate or greater intensity at least 2 days/week.

Asked why the guidelines are sticking with time-based physical activity recommendations in an era when popular smartwatches and other mobile devices can readily spit out number of steps walked, calories burned, and heart-rate data, cardiologist William E. Kraus, MD, 1 of the 17 members of the scientific advisory committee who reviewed and graded the scientific evidence on physical activity, sedentary behavior, and health, answered. He said the group’s careful review concluded that “there’s just not enough evidence at this time to make a recommendation” with regard to mobile device–based measurements of physical activity and their relationship with health benefits.

“We’re hoping to spur more research in this area, so that the next time we make recommendations, that can be incorporated,” added Dr. Kraus, a professor of medicine and cardiologist at Duke University, Durham, N.C., as well as president-elect of the American College of Sports Medicine.

What’s new in the guidelines

This edition tells us that it’s easier to meet the recommendations in the physical activity guidelines,” according to Adm. Giroir. “The new guidelines demonstrate, based on the best science, everyone can dramatically improve their health just by moving: anytime, anywhere, and by any means that gets you active.” He broke the guidelines down as follows:

• “We have new evidence about the risks of sedentary behavior, and new evidence that any amount – any amount – of moderate to vigorous physical activity, like walking, dancing, line dancing if you’re from Texas, and household chores is beneficial,” Adm. Giroir observed.

• While the first edition of the federal guidelines cited strong evidence that physical activity reduces the risk of two types of cancer, breast and colon, the intervening decade has brought forth strong evidence of a protective effect against an additional six types of cancer: bladder, endometrial, kidney, stomach, esophageal, and lung cancer.

• The guidelines formulate for the first time physical activity standards for children ages 3-5 years. The recommended target is at least 3 hr/day of varied physical activity, consistent with existing guidelines in Australia, Canada, and the United Kingdom.

• Updated recommendations for children aged 6-17 years call for an hour or more/day of moderate- or vigorous-intensity physical activity on a daily basis, with that activity level falling within the vigorous category on at least 3 days/week. Plus, it recommends bone- and muscle-strengthening activity on at least 3 days.

• The pediatric guidelines are linked to a planned HHS national strategy to expand children’s participation in youth sports as part of an effort to curb childhood obesity. “We’ll soon announce funding opportunities for communities to increase participation in sports among children and teens through participation in affordable programs with trained coaches,” said Dr. Giroir, a pediatrician.

“I strongly believe our schools should take action to implement this approach. There is a lot of interest right now to effect change in the schools across our country. Part of the answer, I think, is to provide kids with high-quality physical education, but I think we recognize that alone will not be enough,”

The comprehensive school activity model calls for not only enriching school PE programs but also incorporating active transport to school, classroom activity, active learning, and after school programs – activity in all settings during the school day. “I’m very hopeful that this model, which is endorsed in the guidelines document, will be widely adopted by schools in this country over the next decade,” Dr. Giroir said.

The first edition declared that only bouts of physical activity of at least 10 minutes duration should count toward meeting the guidelines. That requirement is gone in the second edition. It was an impediment to being active, and upon close examination it wasn’t based on scientific evidence. That means taking the stairs instead of the escalator or parking farther away from the store count toward the weekly physical activity goal, Dr. Kraus said.

“It makes it easier to achieve the guidelines and to encourage Americans to move more and sit less just by making a better choice at many times during the day,” observed Dr. Giroir, a four-star admiral in the U.S. Public Health Service Commissioned Corps.

The latest guidelines contain up-to-date information on the benefits of regular physical activity in terms of brain health, including reduced risk of developing Alzheimer disease, and improved cognition, including performance on academic achievement tests and measures of executive function, memory, and processing speed, in preadolescent children as well as older adults. Solid evidence also is cited for improved cognition in patients with MS, dementia, ADHD, and Parkinson’s disease.

The guidelines provide new recommendations for physical activity for women during pregnancy and postpartum.

A section of the guidelines is devoted to proven evidence-based strategies to promote physical activity at the individual, small-group, and community level.

Physicians now have a resource to aid them in prescribing an individualized physical activity prescription for their patients with existing health conditions, including osteoarthritis, type 2 diabetes, cancer survivors, and physical disabilities.

The new physical activity guidelines and related resources for health care professionals are available at the Health.gov website.

SOURCE: Giroir BP. AHA scientific sessions, Session ME.05.
**INDICATION FOR TRELEGY**
- 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 FOR TRELEGY**

**CONTRAINDICATIONS**
- TRELEGY is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol, or any of the excipients.

**WARNINGS AND PRECAUTIONS**
- TRELEGY is not for treatment of asthma. LABA monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- TRELEGY should NOT be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- 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 beta₂-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.

**SECONDARY ENDPOINT: CHANGE FROM BASELINE IN TROUGH FEV₁ AT MONTH 12¹,²**

- **STUDY DESCRIPTION¹,²**
  Results of a 12-month, randomized, double-blind, parallel-group study in 10,355 patients with COPD (mean age: 65 years) with a history of moderate or severe COPD exacerbations. At screening, patients had a mean postbronchodilator percent predicted FEV₁ of 45.5% and a mean postbronchodilator FEV₁/FVC ratio: 0.47. Treatment with TRELEGY (n=4145) once daily resulted in statistically significant differences in the co-primary endpoints of reduction in the annual rate of on-treatment moderate to severe exacerbations at Week 52 compared to patients treated with FF/VI 100/25 (0.91 vs 1.07, 15% reduction; P<0.001; n=4133) and with UMEC/VI 62.5/25 (1.21, 25% reduction; P<0.001; n=2069).

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

COPD=chronic obstructive pulmonary disease; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ICS=inhaled corticosteroid; LABA=long-acting beta₂-adrenergic agonist; LAMA=long-acting muscarinic antagonist; UMEC=umeclidinium; VI=vilanterol.

**IN PATIENTS WITH A HISTORY OF COPD EXACERBATIONS**

TRELEGY significantly improved lung function vs FF/VI (an ICS/LABA) and vs UMEC/VI (a LAMA/LABA)

<table>
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<tr>
<th>IMPROVEMENT</th>
<th>TRELEGY (n=3366) 94 mL vs FF/VI (n=3060) -3 mL</th>
<th>TRELEGY (n=3366) 94 mL vs UMEC/VI (n=1490) 40 mL</th>
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<td>97 mL</td>
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10,000+ PATIENTS. 52 WEEKS. 1 LANDMARK STUDY.
TRELEGY significantly improved quality of life in patients with a history of COPD exacerbations

SIGNIFICANT IMPROVEMENT IN QOL BASED ON SYMPTOMS, ACTIVITIES, AND IMPACT ON DAILY LIFE

Patients taking TRELEGY were more likely to show an improvement in quality of life total score at 1 year vs FF/VI and vs UMEC/VI as measured by the SGRQ.*

- SGRQ is a validated, respiratory disease-specific, patient-reported instrument across symptoms, activities, and impact on daily life domains.2,3

Responser rate* was statistically significantly greater for TRELEGY.2

**TRELEGY**

42% **vs** 34%  
(odds ratio: 1.41; 95% CI: 1.29, 1.55; *P*<0.001)

**FF/VI**

42% **vs** 34%  
(odds ratio: 1.41; 95% CI: 1.26, 1.57; *P*<0.001)

**UMEC/VI**

42% **vs** 34%  
(odds ratio: 1.41; 95% CI: 1.26, 1.57; *P*<0.001)

*Response defined as a decrease in SGRQ total score from baseline of 4 or more. SGRQ for COPD (SGRQ-C) was used and results were then converted to SGRQ for reporting purposes.

CI=confidence interval; QOL=quality of life; SGRQ=St George’s Respiratory Questionnaire.

IMPORTANT SAFETY INFORMATION FOR TRELEGY (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

- 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.
- 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 long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

Please see additional Important Safety Information for TRELEGY on the following page.

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

TRELEGY ELLIPTA

(fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg inhalation powder)
IMPORTANT SAFETY INFORMATION FOR TRELEGY (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

• 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.
• 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; therefore, monitoring is warranted.
• Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a healthcare provider immediately if signs or symptoms of acute narrow-angle glaucoma develop.
• Use with caution in patients with urinary retention, especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if signs or symptoms of urinary retention develop.
• Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
• Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

Please see additional Important Safety Information for TRELEGY on the previous pages.

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


TRELEGY ELLIPTA was developed in collaboration with INNOVIVA

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Printed in USA. 1006084R0 August 2018
BRIEF SUMMARY
TRELEGY ELLIPTA (fluticasone furoate, umclidinium, and vilanterol inhalation powder), for oral inhalation

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

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

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death
The safety and efficacy of TRELEGY ELLIPTA in patients with asthma have not been established. TRELEGY ELLIPTA is not indicated for the treatment of asthma.

Use of long-acting beta₂-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 beta₂-agonist.

When beginning treatment with TRELEGY, patients who have been taking oral or inhaled, short-acting beta₂-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 beta₂-agonist becomes less effective; or the patient needs more short-acting beta₂-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 Beta₂-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: umclidinium 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 0% for TRELEGY ELLIPTA (n=1,151), 7% for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=1,134), and 5% for umclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Fatal pneumonia occurred in 12 of 4,151 patients (0.3% per 100 patient-years) receiving TRELEGY ELLIPTA, 5 of 4,134 patients (0.17 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (0.29 per 100 patient-years) receiving umclidinium/vilanterol. In a mortality trial with fluticasone furoate/vilanterol with a median treatment duration of 1.5 years in 16,588 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 Tranfering 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 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 [FEV₁]) and/or asthmatic 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.
TRELEGY ELLIPTA (fluticasone furoate, umecclidinium, and vilanterol inhalation powder), for oral inhalation (cont’d)
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 hypercortisolemia and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, appropriate therapy should be considered.

5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of TRELEGY with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, treoleandomycin, 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-, 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 QT 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 hypotension.

In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment major adverse cardiac event, including non-fatal central nervous system hemorrhages and cerebrovascular conditions, non-fatal myocardial infarction (MI), non-fatal acute MI, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per 100 patient-years for TRELEGY ELLIPTA (n=4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg (n=4,134), and 2.2 per 100 patient-years for umecclidinium/vilanterol 62.5 mcg/25 mcg (n=2,070). Adjudicated on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per 100 patient-years) receiving TRELEGY ELLIPTA, 27 of 4,134 patients (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients (0.94 per 100 patient-years) receiving umecclidinium/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, 90 subjects receiving fluticasone furoate 100 mcg, and 99 subjects receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

5.13 Reduction in Bone Mineral Density

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

5.14 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma

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

5.15 Worsening of Urinary Retention

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

5.16 Coexisting Conditions

TRELEGY, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta-, adrenergic 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 abicans 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)]
- Hypercortisolemia and adrenal suppression [see Warnings and Precautions (5.8)]
- Paradoxical bronchospasm [see Warnings and Precautions (5.10)]
- Cardiovascular effects [see Warnings and Precautions (5.12)]
- Reduction in bone mineral density [see Warnings and Precautions (5.13)]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.14)]
- Worsening of urinary retention [see Warnings and Precautions (5.15)]

6.1 Clinical Trials Experience

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

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

Trials 1 and 2

Two 12-week treatment trials (Trial 1 and Trial 2) evaluated the coadministration of umecclidinium + 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 umecclidinium 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 umecclidinium 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
TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation (cont’d)

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Umeclidinium + Fluticasone Furoate/Vilanterol (n=412)</th>
<th>Placebo + Fluticasone Furoate/Vilanterol (n=412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Disguise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trial 3 - Long-term Safety Data

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

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

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

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

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

7.3 Beta-adrenergic Receptor Blocking Agents

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

7.4 Non-Potassium-Sparing Diuretics

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

7.5 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

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

8.2 Lactation

Risk Summary

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

Fluticasone Furoate/Vilanterol

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

Umeclidinium

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in Cmax 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 Vilanterol

The expected signs and symptoms of 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).

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

Instruct patients to seek medical attention immediately if they experience any of the following:
• Decreasing effectiveness of inhaled, short-acting beta₂-agonists
• Need for more inhalations than usual of inhaled, short-acting beta₂-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 Beta₂-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 and contact their healthcare provider right away.

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

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

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

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

Risks Associated With Beta-agonist Therapy
Inform patients of adverse effects associated with beta₂-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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TRELEGY ELLIPTA was developed in collaboration with INNOCIVA

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Research Triangle Park, NC 27709
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Revised 04/2018
TRL:3BRS

Scan this code to see if your patients may be right for TRELEGY
Palliative care update highlights role of nonspecialists

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

The new edition of national palliative care guidelines provides updated clinical strategies and guidance relevant to all clinicians providing care for critically ill patients, not just those clinicians actively specialized in palliative care. The Clinical Practice Guidelines for Quality Palliative Care, 4th Edition, emphasizes the importance of palliative care provided by “clinicians in primary care and specialty care practices, such as oncologists,” the authors stated. The latest revision of the guideline aims to establish a foundation for “gold-standard” palliative care for people living with serious illness, regardless of diagnosis, setting, or age, according to the National Coalition for Hospice and Palliative Care, which published the clinical practice guidelines.

The update was developed by the National Consensus Project for Quality Palliative Care (NCP), which includes 16 national organizations with palliative care and hospice expertise, and is endorsed by more than 80 national organizations, including the American Society of Hematology and the Oncology Nurses Society.

One key reason for the update, according to the NCP, was to acknowledge that today’s health care system may not be meeting patients’ palliative care needs.

The guidelines call on all clinicians who are not palliative specialists to integrate palliative care principles into their routine assessment of seriously ill patients with conditions such as heart failure, lung disease, and cancer.

This approach differs from the way palliative care is traditionally practiced, often by fellowship-trained physicians, trained nurses, and other specialists who provide that support. The guidelines are organized into sections covering palliative care structure and processes, care for the patient nearing the end of life, and specific aspects of palliative care, including physical, psychological, and psychiatric; social; cultural; ethical, and legal; and spiritual, religious, and existential aspects.

“The expectation is that all clinicians facing serious illness will integrate palliative care competencies, such as safe and effective pain and symptom management and expert communication skills in their practice, and palliative care specialists will provide expertise for those with the most complex needs,” the authors wrote.

These new guidelines represent a “blueprint for what it looks like to provide high-quality, comprehensive palliative care to people with serious illness,” said Thomas W. LeBlanc, MD, who is a medical oncologist, palliative care physician, and patient experience researcher at Duke University, Durham, N.C.

“Part of this report is about trying to raise the game of everybody in medicine and provide a higher basic level of primary palliative care to all people with serious illness, but then also to figure out who has higher levels of needs where the specialists should be applied, since they are a scarce resource,” said Dr. LeBlanc.

An issue with that traditional model is a shortage of specialized clinicians to meet palliative care needs, said Dr. LeBlanc, whose clinical practice and research focuses on palliative care needs of patients with hematologic malignancies.

ICU-acquired pneumonia death risk may be underestimated

**BY TED BOSWORTH**
**MDedge News**

In a large prospectively collected database, the risk of death at 30 days in ICU patients was far greater in those with hospital-acquired pneumonia (HAP) than in those with ventilator-associated pneumonia (VAP) even after adjustment for prognostic factors, according to a large study that compared mortality risk for these complications.

The data for this newly published study were drawn from an evaluation of 14,212 patients treated at 23 ICUs participating in a collaborative French network OUTCOMEREA and published Critical Care Medicine.

HAP in ICU patients “was associated with an 82% increase in the risk of death at day 30,” reported a team of investigators led by Wafa Ibn Saied, MD, of the Université Paris Diderot. Although VAP and HAP were independent risk factors (P both less than .0001) for death at 30 days, VAP increased risk by 38%, less than half of HAP, which increased risk by 82%.

From an observational but prospective database initiated in 1997, this study evaluated 7,735 ICU patients at risk for VAP and 9,747 at risk for HAP.

Of those at risk, defined by several factors including an ICU stay of more than 48 hours, HAP developed in 8% and VAP developed in 1%.

The 30-day mortality rates at 30 days after pneumonia were 23.9% for HAP and 28.4% for VAP. The greater risk of death by HR was identified after an analysis that adjusted for mortality risk factors, the adequacy of initial treatment, and other factors, such as prior history of pneumonia.

In HAP patients, the rate of mortality at 30 days was 32% in the 75 who were reintubated but only 16% in the 101 who were not. Adequate empirical therapy within the first 24 hours for HAP was not associated with a reduction in the risk of death.

As in the HAP patients, mortality was not significantly higher in VAP patients who received inadequate empirical therapy.

Previous studies have suggested that both HAP and VAP increase risk of death in ICU patients, but the authors of this study believe that the relative risk of HAP “is underappreciated.” The researchers had no disclosures.

SLEEP MEDICINE

Is metabolic syndrome really circadian syndrome?

BY DOUG BRUNK
MDedge News

LOS ANGELES – In the opinion of Paul Zimmet, MD, PhD, the Western 24/7 lifestyle is plagued by chronic sleep insufficiency, continual caloric excess, modernization, and globalization, which all can cause disruption of circadian rhythm.

This scenario created the “perfect storm” for rising rates of metabolic syndrome, which is related to low HDL cholesterol levels, central obesity, hypertension, hyperglycemia, and high triglyceride levels. Dr. Zimmet said at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease. These cardiometabolic risk factors “all seem to cluster together in relation to the changes in our society,” he said. “It’s on that basis and research findings that I think we should understand that most of them, if not all, have been demonstrated to relate to circadian rhythm disturbance.”

In fact, the associated comorbidities sleep apnea, depression, and fatty liver disease should be included in the metabolic syndrome cluster and should be renamed the cluster and be renamed the “circadian syndrome,” according to Dr. Zimmet, professor of diabetes at Monash University, Melbourne.

The term metabolic syndrome is anathema, he said. “There have been numerous different definitions, which finally led to an effort to come up with a harmonized definition” by the International Diabetes Federation Task Force on Epidemiology and Prevention, with involvement from the American Heart Association (Circulation. 2009;120[16]:1640-5).

In the early 1970s, Dr. Zimmet and his colleagues at Guys Hospital in London reported on diurnal variation in glucose tolerance. “If you did a glucose tolerance test in the afternoon it could be diabetic, whereas in the morning it was normal,” he noted. “Other researchers reported similar findings. That created in my own mind interest in this area of circadian rhythm. However, I had neglected this until recently, when I was doing background research while trying to find an answer to the elusive question of a central uniting explanation for the cardiometabolic cluster constituting the metabolic syndrome.” So decades later, Dr. Zimmet extended his research to include epigenetics in the quest. Described as the study of heritable changes in function that occur without a change in the sequence of the DNA, epigenetic changes “are closely linked to the circadian rhythm, otherwise known as ‘the body clock,’” said Dr. Zimmet, who also is codirector with Naftali Stern, MD, of the Sagol Center for Epigenetics of Metabolism and Aging at Tel Aviv Medical Center.

He said, “Many aspects of human behavior and metabolism are closely linked to the circadian clock and affected by its rhythm disturbance. We decided that we wanted to further investigate this area: To what extent is circadian rhythm the central feature to explain the clustering of all of these cardiovascular and metabolic risk factors of the metabolic syndrome.”

In recent years, he has been collaborating with Noga Kronfeld-Schor, PhD, of the department of zoology at Tel Aviv University. The research focuses on a gerbil from the Negev: Psammomys obesus (otherwise known as the Israeli fat sand rat), which develops elevated blood sugar, obesity, depression, sleep disturbance, fatty liver, and circadian dysrhythmia when removed from the desert environment to the laboratory. “These are all key features of type 2 diabetes in humans,” he said. “This is probably the best animal model of type 2 diabetes, and we felt that it was worth looking more closely to see if there was a similar relationship in humans as to whether circadian dysrhythmia would be causing all or most of these features in humans including obesity.” An epigenetic study of the gerbil in the laboratory of Prof. Sam El-Osta, also of Monash, has shown that parental diet during early life regulated expression of genes associated with DNA methylation in the key FTO gene associated with obesity (Int J Obesity. 2016;40:1079-88). It suggests that diet-induced metabolic changes can be transmitted from parent to offspring by mechanisms under epigenetic control.

Published studies from other research groups support the link between other of the cardiometabolic metabolic syndrome characteristics, epigenetic modifications, and circadian dysrhythmia including cardiovascular regulation and disease (Eur Heart J. 2018;39[14]:2326-9), sleep loss and alterations in DNA methylation (Science Advances 2018;4[8]:eaar8590), and circadian dysrhythmia and fatty liver (Cell Metab. 2012;15[6]:848-60). “In 2009, the FDA approved bromocriptine mesylate, a drug which has effects on circadian rhythm, for treatment of type 2 diabetes, suggesting its use in diabetes may have some role through the alteration of circadian rhythm,” continued Dr. Zimmet, who also is honorary president of the International Diabetes Federation. “Depression is also clearly linked to circadian rhythm and there is evidence from research and human studies that light therapy may be an effective treatment for type 2 diabetes and depression.”

Dr. Zimmet ended his presentation with a strong call for adding sleep apnea, fatty liver, and depression to the existing features of the metabolic syndrome “to encourage clinicians and researchers to look at the picture of cardiometabolic risk much more broadly than as just a group of metabolic abnormalities,” he said. “We propose that these comorbidities be embraced within the definition of the cardiometabolic cluster and be renamed the ‘circadian syndrome.’ This cluster is now the main driver of the global chronic disease epidemic and its health burden. This is a disease of civilization – the result of the way we live.”

Dr. Zimmet reported having no disclosures.
Veterans living with comorbid traumatic brain injury (TBI) and posttraumatic stress disorder were at increased risk for worse pain and sleep disturbances, reported Nadir M. Balba and colleagues at the VA Portland (Ore.) Health Care System.

The authors conducted a retrospective review of medical records at the VA Portland Health Care System (VAPORHCS) that evaluated 639 veterans who were referred to the VAPORHCS Sleep Disorders Clinic between May 2015 and November 2016. They wrote, “The purpose of this study was to determine whether Veterans with comorbid TBI and PTSD exhibit a higher prevalence of sleep disturbances (determined via self-report and objective polysomnography) and pain compared to Veterans with only TBI or PTSD.”

Patients were recruited to participate in the cross-sectional study, which included participation in an overnight sleep clinic as well as patient self-reported sleep quality, pain, and TBI and PTSD symptom severity. Sleep disturbances included insomnia, nightmares, sleep fragmentation, obstructive sleep apnea, and parasomnias. The survey tools used in the study included the Rivermead Post Concussion Questionnaire (RPCQ), the PTSD Checklist DSM-5 (PSTD-5), the Insomnia Severity Index (ISI), and the Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10). Sleep studies were recorded using Polysmith version 9.0 and sleep staging was performed by a certified sleep technician and verified by a board-certified sleep medicine physician.

Patients were grouped into one of four trauma exposure classifications based on their prior history of trauma, including neither (n = 383), TBI (n = 67), PTSD (n = 126), and TBI+PTSD (n = 63).

Self-reported sleep disturbance, which was the worst among those with PTSD and those with comorbid TBI and PTSD, indicated that PTSD plays a more significant role in the occurrence of disturbed sleep than TBI, the researchers noted. “Participants in the TBI+PTSD and PTSD groups had significantly worse ISI scores (i.e., higher scores) compared to both the TBI and neither groups (P less than .001). Furthermore, participants in the TBI+PTSD and PTSD groups had significantly worse FOSQ-10 scores (i.e., lower scores) compared to both the TBI and neither groups (P less than .001),” they wrote.

In terms of pain, patients with comorbid TBI and PTSD reported the greatest severity of pain, including more frequent headaches and worse photo and phono sensitivities. The TBI and PTSD groups, however, both scored significantly higher in their pain reports than those in the neither group, which suggests “that each of these conditions independently contributes to increased pain,” the authors observed. Ultimately, they cited multiple linear regression models, which attributed sleep disturbances and TBI symptom severity as the primary contributors to pain presentation.

“It is well established that sleep disturbances and pain are inextricably linked,” they said. The results of this study serve to validate that connection “but also suggest this link may be even stronger in those with comorbid TBI and PTSD,” they added.

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Nocturnal hypoxemia predicts incident atrial fibrillation in sleep apnea patients

BY JEFF CRAVEN
MDedge News

Researchers have found a significant independent association between nocturnal hypoxemia and risk of incident atrial fibrillation (AF) in patients with obstructive sleep apnea (OSA), which they believe may help prevent the development of AF in this population, according to recent research published in the journal CHEST.

“These findings are consistent with those of previous studies suggesting that these groups, who are typically at somewhat lower risk of [atrial fibrillation], might be especially vulnerable to the effects of [obstructive sleep apnea] and hypoxemia,” Tetyana Kendzerska, MD, PhD, of the University of Ottawa, and her colleagues wrote in their study.

They performed an analysis of 8,256 patients with data linked to a provincial health administrative database who had suspected OSA who underwent a sleep study at a large academic hospital between 1994 and 2010. The patients were median 47 years old; 62% of the cohort were men, 28% had an apnea-hypopnea index (AHI) of greater than 30 events per hour, and 6% spent more than 30% of the time during sleep with less than 90% oxygen saturation.

Overall, 173 of 8,256 patients (2.1%) developed AF during the study period. In patients with suspected OSA and who were arrhythmia free, nocturnal hypoxemia significantly increased the risk of incident hospitalized AF (hazard ratio, 2.47; 95% confidence interval, 1.64-3.71) over median 10 years of follow-up (interquartile range, 7-13 years) after the researchers controlled for age, sex, chronic obstructive pulmonary disease, history of heart failure, smoking status, nocturnal hypoxemia, and pulmonary embolism, and this association remained significant after adjustment for body mass index and hypertension (HR, 1.77; 95% CI, 1.15-2.74).

“These findings support a relationship between OSA, chronic nocturnal hypoxemia, and the development of [atrial fibrillation], and may be used to identify those patients with OSA who are at greatest risk of developing AF,” Kendzerska and her colleagues wrote in their study.

The researchers cited self-report data as a possible study limitation. They also conceded that comorbid depression and substance use disorder could both play a role in further exacerbating sleep disturbance and pain.

Future research should evaluate how TBI and PTSD, along with other unidentified comorbid conditions, may work together in exacerbating symptoms so that more effective treatment interventions can be developed to address sleep and pain disturbance following multiple traumas.

The authors had no relevant financial disclosures to report.

SLEEP MEDICINE

Single-item scale effective for assessing sleep quality

BY MADHU RAJARAMAN
MDedge News

The single-item sleep quality scale (SQS) produced favorable results comparable to other complex, time-intensive assessment tools, according to findings published in the Journal of Clinical Sleep Medicine.

Sleep evaluation is of primary importance in many clinical research contexts, yet “despite their utility in the measurement of sleep quality [sleep assessment tools] are prone to several limitations when used in the context of clinical trials and may not always fulfill industry standards. For example,” the Pittsburgh Sleep Quality Index (PSQI) “… was developed as a screening tool and may not be sensitive enough for detecting treatment differences in clinical trials.”

In a study of 70 insomnia patients and 651 depression patients, concurrent criterion validity analysis yielded strong correlations between the SQS and the morning-questionnaire insomnia (MQI) and PSQI in patients with insomnia and depression, respectively. The investigators wrote, “The single-item format enables a patient-reported rating of sleep quality over a 7-day recall period without greatly increasing the patient’s burden. The use of a discretizing visual analog scale (VAS) increases the potential for a more sensitive measurement.” The SQS is a quick but accurate self-reported assessment of sleep quality.

The SQS was validated based on two studies. Eligible patients in the 4-week, randomized, multicenter insomnia study were aged 30–75 years and were receiving a Food and Drug Administration–approved hypnotic agent as usual treatment for insomnia based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The MQI was used daily for the duration of the study, wrote Ellen Snyder, PhD, of Merck, in Kenilworth, N.J., and her coauthors.

The depression study was a randomized, double-blind, parallel-group, 12-month international trial evaluating the safety of the substance P antagonist aprepitant, compared with paroxetine hydrochloride. Patients were aged 18 years or older, with a DSM-IV diagnosis of major depressive disorder. Patients completed the SQS and PSQI at baseline, week 1, and week 8.

In insomnia patients, a Pearson correlation of 0.76 was found at week 1 for the SQS in relation to the MQI. In patients with depression, Goodman-Kruskal correlation coefficients for the SQS in relation to the Pittsburgh Sleep Quality Index (PSQI) were –0.87, –0.88, and –0.92 at baseline, week 1, and week 8, respectively. Correlations were negative because “better sleep quality is associated with a lower score on the MQI and PSQI, but a higher score on the SQS,” the authors noted.

The results support the use of the SQS as a “practical sleep measure that can effectively gauge sleep quality without significantly increasing the burden of clinical trial participants,” they added.

Funding for the study was provided by Merck Sharp & Dohme.


OSA linked to resistant hypertension in black patients

BY MADHU RAJARAMAN
MDedge News

Untreated moderate or severe obstructive sleep apnea (OSA) was associated with greater odds of resistant hypertension in black patients, according to findings published in Circulation.

In an analysis of 664 patients with hypertension, those with moderate to severe OSA had twofold higher odds of resistant hypertension, compared with those with no or mild OSA (odds ratio, 2.04; 95% confidence interval, 1.14–3.67), reported Dayna A. Johnson, PhD, of the Division of Sleep and Circadian Disorders at Brigham and Women’s Hospital, Boston, and coauthors.

Participants were enrolled in the JHSS, an ancillary trial conducted during December 2012 – May 2016 as part of the Jackson (Miss.) Heart Study, a longitudinal study of 5,306 black adults aged 21-95 years. Patients included in the analysis had hypertension (defined as high blood pressure, use of antihypertensive medication, or self-reported diagnosis). Those without a valid in-home sleep apnea test and with missing data on hypertension, measured blood pressure, or use of antihypertensive medications and diuretics were excluded from analysis.

Sleep apnea was assessed using measures of nasal pressure, thoracic and abdominal inductance plethysmography, finger pulse oximetry, body position, and electrocardiography with a validated Type 3 home sleep apnea device. Obstructive apneas were identified as a flat or nearly flat amplitude of the nasal pressure signal for greater than 10 seconds, accompanied by respiratory effort on the abdominal or thoracic inductance plethysmography bands. Severity was defined by the standard Respiratory Event Index (REI) categories: fewer than 5 events (unaffected), greater than or equal to 5 events to fewer than 15 events (mild), greater than or equal to 15 events to fewer than 30 events (moderate), and greater than or equal to 30 events (severe), the authors reported.

High blood pressure (BP) was defined as systolic BP greater than or equal to 130 mm Hg or diastolic BP greater than or equal to 80 mm Hg. Controlled hypertension was defined as systolic BP less than 130 mm Hg and diastolic BP less than 80 mm Hg. Uncontrolled BP was defined as high BP with use of one or two classes of antihypertensive medications; resistant hypertension was defined as having high BP while on greater than or equal to three classes of antihypertensive medications with one being a diuretic or as using of greater than four classes of antihypertensive medications regardless of BP control, Dr. Johnson and colleagues reported.

A total of 25.7% of hypertension patients had moderate or severe OSA, though only 6% of these patients had an OSA diagnosis from a physician. In addition, 48.2% of patients had uncontrolled hypertension, and 14.5% had resistant hypertension.

Moderate or severe OSA was associated with nearly twofold higher unadjusted odds of resistant hypertension (OR, 1.92; 95% CI, 1.15-3.20). In adjusted models, moderate or severe OSA and nocturnal hypoxemia were not associated with uncontrolled hypertension but were associated with resistant hypertension (OR, 2.04; 95% CI, 1.14-3.67; OR, 1.25; 95% CI, 1.01-1.55, respectively).

Compared with no OSA, severe OSA was associated with more than three times higher odds of resistant hypertension (OR, 3.50; 95% CI, 1.54-7.91). This association was even higher after adjustment for covariates (OR, 3.58; 95% CI, 1.39-9.19).

“These data suggest that untreated OSA may contribute to the high burden of resistant hypertension in blacks,” Dr. Johnson and coauthors wrote. “Future studies should test whether diagnosis and treatment of OSA may be interventions for improving BP control” and reducing this burden, they added.

“These findings are particularly important given that most adults with OSA are undiagnosed and untreated.”

The study was funded by grants from the National Heart, Lung, and Blood Institute. One of the authors reported receiving funding from Amgen. No other disclosures were reported.

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.
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.
**1. INDICATIONS AND USE**

**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 therapy 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 12 years and older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.

**2. CONTRAINDICATIONS**

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

**3. WARNINGS AND PRECAUTIONS**

**3.1 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 did not discontinue 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 serum sickness-like reactions.

**3.2 Conjunctivitis and Keratitis**

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT compared to 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 (6.5)]. Keratitis was reported in <1% of the DUPIXENT group (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 group (12 per 100 subject-years) and in 0% of the placebo + TCS group (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 (6.6)]. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

**3.3 Eosinophilic Conditions**

Patients being treated for asthma may present with severe 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 visualising rash, worsening pulmonary symptoms, cardiac complications, and/or neurophy in presenting in their patients with eosinophils. 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.

**3.4 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.

**3.5 Reduction of Corticosteroid Dosage**

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose may be associated with systemic withdrawal symptoms and/or of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be done at a slower rate than in their respective comparator groups during the first 16 weeks of treatment.

**4. 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 (5.5)]

**5.1 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 trials, 1472 subjects were treated with DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 738 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 24. Trial 3 compared the safety of DUPIXENT plus TCS to placebo plus TCS through Week 52.

**Weeks 1 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 at least 1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapy*</th>
<th>DUPIXENT + TCS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>51 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11 (2)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (1)</td>
<td>0 (1)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (1)</td>
<td>0 (2)</td>
</tr>
</tbody>
</table>

*Pooled analysis of Trials 1, 2, and 4

**4. CONTRAINDICATIONS**

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

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=34) 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 FEV₁ (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)].

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.

8.6 Pregnancy

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 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 the dosage requirements.

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)].

Contraindications 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 (5.4)].
Parents who delay immunization may have less trust in vaccines, may have done research in their own social networks, and may present alternatives to a standard immunization schedule or want to omit certain vaccines from their child's immunization schedule, he noted. Using the analogy of a car seat is one approach to identify the importance of vaccination to these parents: "Waiting to give the shots is like putting your baby in the car seat after you've already arrived at the store – the protection isn't there for the most important part of the journey!"

In cases where parents refuse vaccination, you should not expect to change a parent's mind in a single visit, but instead focus on building the patient-provider bond. However, presenting information the parent may have already seen, such as vaccination data from the Food and Drug Administration or Centers for Disease Control and Prevention, may alienate parents who identify with groups that share vaccine-hesitant viewpoints and erode your ability to persuade a parent's intent to vaccinate.

A study by Nyhan et al. randomized parents to receive one of four pieces of interventions about the MMR vaccine: information from the CDC explaining the lack of evidence linking autism and the vaccine, information about the dangers of the diseases prevented by the vaccine, images of children who have had diseases prevented by the vaccine, and a "dramatic narrative" from a CDC fact sheet about a child who nearly died of measles. The researchers found no informational intervention helped in persuading to vaccinate in parents who had the "least favorable" attitudes toward the vaccine. And in the case of the dramatic narrative, there was an increased misperception about the MMR vaccine (Pediatrics. 2014;133[4]:e835-42).

Dr. Hempstead and Dr. Saba outlined four rhetorical devices to include in conversations with parents about vaccination: cognitive ease, natural assumption, an appeal to identity, and use of advantageous terms.

**Cognitive ease**
Cognitive ease means creating an environment in which the patient is relaxed, comfortable, and more likely to be agreeable. Recognize when the tone shifts, and strive to maintain this calm and comfortable environment throughout the discussion. "If your blood pressure is coming up, that means theirs is, too," Dr. Hempstead said.

**Natural assumption**
How you are offering the vaccination also matters, he added. Rather than asking whether a patient wants to vaccinate ("Have you thought about your flu vaccine this year?") instead frame the discussion with vaccination as the default option ("Is your child due for a flu vaccination this year? Yes, he is. Let's get that taken care of today."). Equating inaction with vaccination prevents the risk fallacy phenomenon from occurring in which, when given multiple options, people give equal weight to each option and may choose not to vaccinate, Dr. Hempstead noted.

Dr. Saba cited research that backed this approach. In a study by Opel et al., using a "presumptive" approach instead of a "participatory" approach when discussing a provider's recommendation to vaccinate helped. The presumptive conversations had an odds ratio of 17.5, compared with the participatory approach. In cases in which parents resisted the provider's recommendations, 50% of providers persisted with their original recommendations, and 47% of parents who initially resisted the recommendations agreed to vaccinate (Pediatrics. 2013;132[6]:1037-46).

**Appeal to identity**
Another strategy to use is appealing to the patient's identity as a good parent and link the concept of vaccination with the good parent identity. Forging a new common identity with the parents through common beliefs – such as recognizing that networks to which parents belong are an important part of his or her identity – and reemphasizing the mutual desire to protect the child is another strategy.

**Using advantageous terms**
Positive terms, such as "protection," "health," "safety," and "what's best," are much better words to use in conversation with parents and have more staying power than negative terms, like "autism" and "side effects," Dr. Hempstead said. "Stay with positive messaging," he said. "Immediately coming back to the positive impact of this vaccine, why we care so much, why we're doing this vaccine, is absolutely critical."

Dr. Hempstead and Dr. Saba reported no relevant conflicts of interest.
REVATIO OS gives you another option to help patients make strides.

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

Prescribe the form that best meets your patients’ needs.

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

REVATIO 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.

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.

Indication

REVATIO is a phosphodiesterase-5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) 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 (23%).

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, rifampin, rifavirin, and ribavirin 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.

The Revatio Family

Available in OS, tablet, and injection forms.

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

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INDICATION AND USAGE

REVATIO is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) Group 1 in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominantly patients with NYHA Functional Class II symptoms. Efficacies were diastolic (71%) or associated with congestive tissue disease (CCTD) (25%).

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

DOSEAGE AND ADMINISTRATION

REVATIO Tablets and Oral Suspension The recommended dose of REVATIO is 5 mg or 20 mg three times a day. Amoxicillin (500 mg) or metronidazole (400 mg) should be administered for at least 12 hours prior to the dose of REVATIO.

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. Replace the cap. 6. Accurately measure out another 60 mL of water and add it to the bottle. 7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds. 8. Replace the cap. 9. Press the bottle adapter into the neck of the bottle. The adapter is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle. 10. While the expiration date of the constipated oral suspension label, the expiration date of the constipated oral suspension is 60 days from the date of expiration.

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 nitrates, including isosorbide dinitrate or isosorbide mononitrate, 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 arteriovenous fistula). REVATIO may also result in hypotensive responses in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactoid shock and anaphylactic 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 arteriovenous fistula). REVATIO may also result in hypotensive responses in patients with known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension. Hypersensitivity, including anaphylactic reaction, anaphylactoid shock and anaphylactic reaction, has been reported in association with the use of sildenafil.

Visual Loss (Posteriorcyclovascular Occlusive Disease Pulmonary vasodilatorists may significantly worsen the cardiovascular status of patients with pulmonary vaso-occlusive disease (PAH). As a consequence of visual impairment, patients with PAH should be monitored for visual symptoms.

Epiptaxis The incidence of epistaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in patients with PAH (REVATIO 0%, placebo 2%) patients. The incidence of epistaxis was also higher in REVATIO-treated patients with a concomitant oral vitamin K antagonist (8% vs. 2%) in those not treated concomitantly with vitamin K antagonist. The safety of REVATIO is unknown in patients with bleeding disorders or active peptic ulceration.

Vasospastic Lesion Use of pulmonary vasodilatorists increases the risk of developing angina, including angina during exercise, more frequent and unexplained episodes of angina, and increased frequency of angina during exercise. Use of pulmonary vasodilatorists may also result in hypotension, including anaphylactic reaction, anaphylactoid shock and anaphylactic reaction, has been reported in association with the use of sildenafil.

Postmarketing Experience The following adverse reactions have been identified during post approval use of sildenafil (mained by both 50 mg and 100 mg). 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 arrhythmias, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracranial 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 always 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 Seizures, seizure recurrence.
Growing options for treating pediatric asthma with biologics

BY TARA HAELLE

ORLANDO – The goal of treatment is the same for all asthma cases, regardless of severity: “to enable a patient to achieve and maintain control over their asthma,” according to Stanley J. Szefler, MD, a professor of pediatrics at the University of Colorado at Denver.

That goal includes “reducing the risk of exacerbations, emergency department visits, hospitalizations, and progression as well as reducing impairments, including symptoms, functional limitations, poor quality of life, and other manifestations of asthma,” Dr. Szefler, also director of the Children’s Hospital of Colorado pediatric asthma research program, told colleagues at the annual meeting of the American Academy of Pediatrics.

Severe asthma challenges

These aims are more difficult with severe asthma, defined by the World Health Organization as “the current level of clinical control and risks which can result in frequent severe exacerbations and/or adverse reactions to medications and/or chronic morbidity.” Dr. Szefler explained. Severe asthma includes untreated severe asthma, difficult-to-treat asthma, and treatment-resistant severe asthma, whether controlled on high-dose medication or not.

Allergen sensitization, viral respiratory infections, and respiratory irritants (such as air pollution and smoking) are common features of severe asthma in children. Also common are challenges specific to management: poor medication adherence, poor technique for inhaled medications, and undertreatment. Poor management can lead to repeated exacerbations, adverse effects from drugs, disease progression, possible development of chronic obstructive pulmonary disease (COPD), and early mortality.

The National Heart, Lung, and Blood Institute EPR-3 guidelines for treatment of pediatric asthma recommend a stepwise approach to therapy, starting with short-acting beta-agonists as needed (SABA p.r.n.). The clinician then assesses the patient’s symptoms, exacerbations, side effects, quality of life, and lung function to determine whether the asthma is well managed or requires inhaled corticosteroids, or another therapy in moving through the steps. Each step also involves patient education, environmental control, and management of the child’s comorbidities.

It is not until steps 5 and 6 that the guidelines advise considering the biologic omalizumab for patients who have allergies. But other biologic options exist as well. Four biologics currently approved for treating asthma include omalizumab, mepolizumab, benralizumab, and reslizumab, but reslizumab is approved only for patients at least 18 years old.

Biologics for pediatric asthma

Omalizumab, which targets IgE, is appropriate for patients at least 6 years old in whom inhaled corticosteroids could not adequately control the symptoms of moderate to severe persistent asthma. Dosing of omalizumab is a subcutaneous injection every 2-4 weeks based on pretreatment serum IgE and body weight using a dosing table that starts at 0.016 mg/kg per IgE (IU/mL). Maximum dose is 375 mg every 2 weeks in the United States and 600 mg every 2 weeks in the European Union.

The advantages of an anti-IgE drug are its use only once a month and its substantial effect on reducing exacerbations in a clearly identified population. However, these drugs are costly and require supervised injection.

Growing options for treating pediatric asthma with biologics

CONTINUED ON FOLLOWING PAGE

VIEW ON THE NEWS

Susan Millard, MD, FCCP, comments: Dr. Szefler’s talk at the American Academy of Pediatrics National Conference and Exhibition in November 2018 was an excellent review of the exciting new therapies coming to the rescue for severe persistent asthma that is poorly controlled. The next hurdle, though, will be how to get these biologics approved by insurance companies for use in our patients.

Continued on following page
New pediatric therapies show promise for influenza

BY JEFF CRAVEN
MDedge News

ORLANDO – More therapies are becoming available for children for the treatment of influenza and multidrug-resistant infections such as Enterobacteriaceae and Acinetobacter, John S. Bradley, MD, said at the annual meeting of the American Academy of Pediatrics.

Dr. Bradley, director of the division of infectious diseases at Rady Children’s Hospital–San Diego, discussed a therapy for influenza, baloxavir, which was recently approved as a fast-acting single-dose medication and currently is under study in children. Also, a recent double-blind, phase 3 trial in the New England Journal of Medicine recruited patients as young as 12 years old. In the study, patients in the intervention group resolved their fever in median 25 hours, compared with 42 hours in the placebo group. Baloxavir better reduced viral load at day 2, compared with oseltamivir and placebo, but there was a similar alleviation of symptoms between both groups. There was a greater incidence of nausea and vomiting among the oseltamivir group, while the baloxavir group had a higher rate of diarrhea (N Engl J Med. 2018;379:913-23).

However, Dr. Bradley noted baloxavir is much more expensive than oseltamivir, which may not justify the better tolerance of the drug for influenza treatment.

“You don’t get better with it faster, so I’m not going to be recommending you all run to baloxavir this flu season for kids 12 years of age and older,” Dr. Bradley said. “I think oseltamivir is still fine, unless we end up with oseltamivir resistance.”

Solithromycin, an intravenous and oral fluoroquinolone, has shown promising results against gram-positive and gram-negative pathogens for community-acquired pneumonia and other infections. During the drug’s study period, Cempra sold solithromycin to Melinta. However, one trial showed elevated liver functions in a higher number of patients than expected, and the Food and Drug Administration asked Melinta to conduct additional studies. Investigations on solithromycin have currently stopped until Melinta secures funding. “Until they get better resources, this particular drug is on hold, but you’ll see it again, I’m sure,” said Dr. Bradley, who also is professor and chief of the division of infectious diseases at the University of California, San Diego.

Dr. Bradley also discussed the efficacy of tedizolid, a protein synthesis inhibitor similar to linezolid approved in adults for the treatment of skin infections. He noted tedizolid is more active than linezolid, but the treatment course is a shorter dose for a shorter amount of time. Compared with linezolid, which can cause thrombocytopenia or neutropenia if taken for more than 10 days to 14 days, there also are fewer side effects.

“The tedizolid is much, much safer,” Dr. Bradley said, who added that trials of efficacy for tedizolid are currently underway in pediatric patients. “We’re hoping that will end up being the pediatric oxazolidinone.”

Other investigative therapies approved for adults and under study for use in children include ceftazidime/avibactam for treatment of urinary tract and complicated intra-abdominal infections, which is effective against meropenem-resistant Enterobacteriaceae and resistant Escherichia coli.

Continued from previous page administration, Dr. Szefler noted. They also carry a risk of anaphylaxis in less than 0.2% of patients, requiring the patient to be monitored after first administration and to carry an injectable epinephrine after omalizumab administration as a precaution for late-occurring anaphylaxis.

Mepolizumab is an anti– interleukin (IL)–5 drug used in patients at least 12 years old with severe persistent asthma that’s inadequately controlled with inhaled corticosteroids. Peripheral blood counts of eosinophils determine if a patient has an eosinophilic phenotype, which has the best response to mepolizumab. Dosing is 100 mg subcutaneously every 4 weeks.

For patients with atopic asthma, mepolizumab is effective in reducing the daily oral corticosteroid dose and the number of both annual exacerbations and exacerbations requiring hospitalization or an emergency visit. Other benefits of mepolizumab include increasing the time to a first exacerbation, the preand postbronchodilator forced expiratory volume in 1 second (FEV₁) and overall quality of life. Patient reductions in exacerbations while taking mepolizumab were associated with eosinophil count but not IgE, atopic status, FEV₁, or bronchodilator response in the DREAM study (Lancet. 2012 Aug 18;380[9842]:651-9).

Two safety considerations with mepolizumab include an increased risk of shingles and the risk of a preexisting helminth infection getting worse. Providers should screen for helminth infection and might consider a herpes zoster vaccination prior to starting therapy, Dr. Szefler said.

Benralizumab is an anti–IL5Ra for use in people at least 12 years old with severe persistent asthma and an eosinophilic phenotype (at least 300 cells per microliter). Dosing begins with three subcutaneous injections of 30 mg every 4 weeks, followed by administration every 8 weeks thereafter.

Benralizumab’s clinical effects include reduced exacerbations and oral corticosteroid use, and improved asthma symptom scores and prebronchodilator FEV₁, Higher serum eosinophils and a history of more frequent exacerbations are both biomarkers for reduced exacerbations with benralizumab treatment.

Dulipidum: New kid on the block

The newest biologic for asthma is dulipidum, approved Oct. 19, 2018, by the Food and Drug Administration as the only asthma biologic that patients can administer at home. Dulipidum is an anti–IL-4 and anti–IL-13 biologic whose most recent study results showed a severe exacerbations rate 50% lower than placebo (N Engl J Med. 2018 Jun 28;378[26]:2486-96.). Patients with
Flu vaccine effectiveness drops in children by half after 6 months

BY HEIDI SPLETE
MDedge News

The effectiveness of the influenza vaccine declined significantly after 9 months, according to 5 years of data from approximately 15,000 children in Hong Kong.

The vaccine is known to last less than a year, but the findings support the need for more vaccine availability in areas where influenza activity occurs year-round, wrote Shuo Feng, PhD, and Susan S. Chiu, MD, of the University of Hong Kong, and their colleagues.

In a study published in the Lancet Respiratory Medicine, the researchers reviewed how vaccine effectiveness changed over time by analyzing data from children aged 6 months to 17 years admitted to a Hong Kong hospital between 2012 and 2017. The study population involved 15,695 children hospitalized for respiratory infections, including 2,500 who were positive for influenza A or B and 13,195 who were negative. Of these, 6.4% of the positive patients and 11% of the negative patients had been vaccinated; 70% - 80% of the vaccinations occurred before the end of December of a given year.

Overall, the vaccination-effectiveness rate was 79% for 0.5 to 2 months after vaccination, then dropped to 60% at 2-4 months, 57% at 4-6 months, and 45% at 6-9 months.

The researchers estimated vaccine effectiveness by three time periods: September to December, January to April, and May to August. Across seasons, vaccine effectiveness for all age groups was 79% for September to December, 67% for January to April, and 43% for May to August.

The study results were strengthened by the inclusion of year-round activity, but limited by several factors including lack of data on patients’ vaccination history and the specifics of each year’s flu virus, and lack of generalizability to an adult population, the researchers said.

However, the findings support data from previous studies on the effectiveness of annual vaccination, with the optimal timing from October to December in Hong Kong, they said. “Improved influenza vaccines are needed to provide year-round protection for children, particularly in subtropical and tropical locations,” they added.

The study was supported by the Health and Medical Research Fund and the Research Grants Council, Hong Kong. The lead authors had no financial conflicts to disclose.


Continued from previous page

higher baseline levels of eosinophils had the best response, although some patients showed hypereosinophilia following dupilumab therapy. The study had a low number of adolescents enrolled, however, and more data on predictive biomarkers are needed. Dupilumab also requires a twice-monthly administration.

“It could be potentially better than those currently available due to additional effect on FEV1,” Dr. Szefler said, but cost and safety may determine how dupilumab is recommended and used, including possible use for early intervention.

“Look at asthma in children as a chronic disease that can result in potentially preventable adverse respiratory outcomes in adulthood,” Dr. Szefler said. Dr. Szefler has served on the advisory board for Regeneron and Sanofi, and he has consulted for AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Novartis, and Propeller Health.

chestphysiciannews@chestnet.org
Digital alerts reduced AF-related stroke, MI rates

BY RICHARD MARK KIRKNER
MDedge News

CHICAGO – High-risk hospitalized patients with atrial fibrillation (AF) whose doctors monitored them with a computerized alert system were more than twice as likely to be on anticoagulation and had significantly lower rates of death and other cardiovascular events, compared with patients on a standard admissions protocol, according to results of a randomized, controlled trial presented at the American Heart Association scientific sessions.

“Alert-based computerized decision support [CDS] increased the prescription of anticoagulation for stroke prevention in atrial fibrillation during hospitalization, at discharge, and at 90 days after randomization in high-risk patients,” said Gregory Piazza, MD, of Brigham and Women’s Hospital, Boston, in presenting results of the AF-ALERT trial. “The reduction in major cardiovascular events was attributable to reductions in MI and stroke/transient ischemic attack at 90 days in patients whose physicians received the alert.”

The trial evaluated 458 patients hospitalized for AF or flutter and with CHA2DS2-VASc scores of 1-8 randomly assigned to the alert (n = 258) or no-alert (n = 210) groups.

Dr. Piazza explained that, for those in the alert group, the CDS system notified physicians when the patient’s CHA2DS2-VASc score increased. From there, the physician could choose to open the stroke-prevention order set, a very tiny percentage elected to read the AF guidelines, and about 64% exited but provided a rationale for omitting anticoagulation,” Dr. Piazza noted.

The alert group was far more likely to be prescribed anticoagulation during the hospitalization (25.8% vs. 9.5%; P < .0001), at discharge (23.8% vs. 12.9%; P = .003), and at 90 days (27.7% vs. 17.1%; P = .007) than the control group. The alert resulted in a 55% relative risk reduction in a composite outcome of death, MI, cerebrovascular event, and systemic embolic event at 90 days (11.3% vs. 21.9%; P = .002).

The alert group had an 87% lower incidence of MI at 90 days (1.2% vs. 8.6%, P = .0002) and 88% lower incidence of cerebrovascular events or systemic embolism at 90 days (0% vs. 8.6% in the control group).

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OFEV SLOWS THE PATH OF
REDUCED LUNG FUNCTION DECLINE
OFEV significantly reduced the annual rate of FVC decline by ~50% across 3 clinical trials.

INDICATION
OFEV (nintedanib) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hepatic Impairment

• OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Elevated Liver Enzymes and Drug-Induced Liver Injury

• Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the post-marketing period, non-serious and serious cases of DILI, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. The majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN.

• Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.

• Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.
Please see additional Important Safety Information and accompanying Brief Summary of Prescribing Information on the following pages.

**IPF PROGRESSION**

**DEMONSTRATED SAFETY AND TOLERABILITY PROFILE**

In 3 clinical trials, the most common adverse events were gastrointestinal in nature and generally of mild to moderate intensity.

*Results from 3 randomized, double-blind, placebo-controlled trials investigating the effect of OFEV in patients with IPF over 52 weeks. The annual rate of FVC decline was the primary endpoint and the time to first acute IPF exacerbation was a secondary endpoint. INPULSIS®-1 (Study 2) included 309 patients in the OFEV arm, 204 patients in the placebo arm; INPULSIS®-2 (Study 3) included 329 patients in the OFEV arm, 219 patients in the placebo arm; and TOMORROW (Study 1) included 85 patients in the OFEV 150-mg bid arm, 85 patients in the placebo arm.

**IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)**

**Gastrointestinal Disorders**

**Diarrhea**

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and less than 1% in placebo patients, respectively.

Please see additional Important Safety Information and accompanying Brief Summary of Prescribing Information on the following pages.

**The alert prompted 35% of physicians to open the stroke-prevention order set. A small percentage elected to read the AF guidelines, and about 64% exited but provided a rationale for omitting anticoagulation.**

Moderator Mintu Turakhia, MD, of Stanford (Calif.) University, questioned the low rate of anticoagulation in the study’s control arm – 9.5% – much lower than medians reported in many registries. He also asked Dr. Piazza to describe the mechanism of action for prescribing anticoagulation in these patients.

Dr. Piazza noted the study population was hospitalized patients whose providers had decided prior to their admissions not to prescribe...
continued from previous page

Regarding the mechanism of action, "the electronic alert seems to preferentially increase the prescription of [direct oral anticoagulants] over warfarin, and that may have been one of the mechanisms," Dr. Piazza said. Another explanation he offered was "off-target" effects whereby, if providers have a better idea of a patient's risk for a stroke or MI, they'll be more aggressive about managing other risk factors. "There are a number of interventions that could be triggered if the alert prompted the provider to have a conversation with patients about their risk of stroke from AF," he said. "This may have impact beyond what we can tell from this simple [Best Practice Advisory in the Epic EHR system]. I think we don't have a great understanding of the full mechanisms of CDS."

Dr. Piazza reported financial relationships with BTG, Janssen, Bristol-Myers Squibb, Daiichi Sankyo, Portola, and Bayer. Daiichi Sankyo funded the trial. Dr. Turakhia reported relationships with Apple, Janssen, AstraZeneca, VA, Boehringer Ingelheim, Cardiva Medical, Medtronic, Abbott, Precision Health Economics, iBeat, iRhythm, MyoKardia, and Biotronik, and an ownership Interest in AliveCor.

chestphysiciannews@chestnet.org

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders (cont’d)
Nausea and Vomiting

• Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV (nintedanib) and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.

• If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use effective contraception during treatment and at least 3 months after the last dose of OFEV. Verify pregnancy status prior to starting OFEV.

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. In the post-marketing period, non-serious and serious bleeding events, some of which were fatal, have been observed.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus 0% placebo patients. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.


ADVERSE REACTIONS

• Adverse reactions reported in greater than or equal to 5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.

• The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

DRUG INTERACTIONS

• P-glycoprotein (P-gp) and CYP3A4 inhibitors and Inducers: Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

• Anticoagulants: Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

• Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.

• Reproductive Potential: OFEV may reduce fertility in females of reproductive potential.

• Smokers: Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

CL-OF-100007 01.29.18

Please see accompanying Brief Summary of Prescribing information on the following pages.
Barbershop BP intervention going strong at 12 months

BY KARI OAKES

A novel intervention that brought training to barbers, and pharmacists to barber-shops, resulted in marked and sustained reduction in blood pressure for a black male cohort of participants, according to 12-month data from the project. Of the 319 black, non-Hispanic male participants, 180 were randomized to participate in an intensive 6-month hypertension intervention. The study protocol allowed pharmacists, who visited participants at their barbershops, to prescribe hypertension medication under collaborative practice agreements with participants’ primary care providers (PCPs). Compared with an active control

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information, including Patient Information.

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests in pregnancy test prior to initiating treatment with OFEV (see Warnings and Precautions).

Recommended Dosage: The recommended dosage of OFEV is 150 mg bid, administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient not to make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg bid, administered approximately 12 hours apart. (see Use in Specific Populations).

Modification Due to Adverse Reactions: In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction is under control. If adverse reaction is severe (grade 3) or if the adverse reaction is severe (grade 4), then treatment should be stopped and the adverse reaction should be managed. In clinical studies, one case of severe gastrointestinal event reported in 2% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to less than 1% of placebo-treated patients. Diagestive modulatory or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea with first signs with adequate hydration and antiarrhythmic medication (e.g., loperamide), and consider treatment interruption if diarrhea continues (see Dosage and Administration). OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. Severe diarrhea persists despite symptomatic treatment, discontinuation of OFEV. Nausae and Vomiting: Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively (see Adverse Reactions). In most patients, these events were mild to moderate in intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 11% of the patients. For nausea or vomiting that persists despite appropriate supportive care including antiemetic therapy, dose reduction or treatment interruption may be required (see Dosage and Administration). OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryofetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and use effective contraception during treatment and at least 1 month after the last dose of OFEV. Verify pregnancy status prior to treatment with OFEV (see Use in Specific Populations).

Arterial Thromboembolic Events: Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 25% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients with higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial infarction. Risk of Bleeding: Based on the mechanism of action (EGFR inhibitor), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the post-marketing period, non-serious and serious bleeding events, some of which were fatal, have been observed. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. Gastrointestinal Perforation: Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV compared to 0 cases in placebo-treated patients. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who may have had recent abdominal surgery, previous history of diverticular disease or receiving concurrent corticosteroids or NSABPs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in detail in other sections of the labeling: Elevated Liver Enzymes and Drug-Induced Liver Injury (see Warnings and Precautions).

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1,000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1 and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for placebo-treated patients. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (2.1% vs. 0.8%) and mycophenolate (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasms malignant (0.3% vs. 0.0%), and myocardial infarction (0.3% vs. 0.0%). A defined category of major adverse cardiovascular events (MACE), including MI, fatal events, was reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reductions in the patients treated with OFEV was diabetes (11%). Arterial hypertension leading to discontinuation were reported in 21% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation at least 1% of the patients treated with OFEV and more than placebo were pneumonia (5.9%), nausea (5.2%), and decreased appetite (2%). The most common adverse reactions with an incidence of greater than or equal to 1% in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OFEV (n=958)</th>
<th>Placebo (n=508)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15%</td>
<td>6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevator enzymes</td>
<td>14%</td>
<td>3%</td>
<td>0.02</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>5%</td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10%</td>
<td>3%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.
In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1% vs. 0.6%). Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. 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: Drug-Induced liver injury [see Warnings and Precautions: Thrombocytopenia]. Non-serious and serious bleeding events, some of which were fatal, have been observed in the postmarketing experience period.

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate for P-gp and CYP3A4. Co-administration with oral doses of a P-gp and CYP3A4 inhibits, ketoconazole, increased exposure to nintedanib by 65%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV [see Dosage and Administration]. Co-administration with oral doses of a P-gp and CYP3A4 inducer, rifampin, decreased exposure to nintedanib by 57%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. Anticoagulants: Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered at the maximum recommended human dose (MRHD) in adults (360 mg/day). Nintedanib decreases post-natal viability of rat pups during the first 4 post-partum days when doses were exposed to less than the MRHD (an AUC at a maternal oral dose of 10 mg/kg/day). Lactation: Risk Summary: There is no information on the effects of nintedanib on the breast milk of women who have lactated. OFEV is excreted in the milk of lactating rats, but there is no information on the concentration of OFEV in human milk. Nintedanib and its metabolites are present in the milk of lactating rats [see Data]. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women not to breastfeed during treatment with OFEV. Single-dose and repeat-dose OFEV plasma concentrations were similar in lactation rats and nursing infants. Concomitant administration of drugs that are highly protein bound may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see Warnings and Precautions].

OVERDOSAGE: In the trials, one patient was inadvertently dosed with OFEV at 150 mg/day for 5 days (rabbit) or 5 times the maximum human dose (adult) in adults (150 mg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-partum days when doses were exposed to less than the MRHD (an AUC at a maternal oral dose of 10 mg/kg/day). Lactation: Risk Summary: There is no information on the effects of nintedanib on the breast milk of women who have lactated. OFEV is excreted in the milk of lactating rats, but there is no information on the concentration of OFEV in human milk. Nintedanib and its metabolites are present in the milk of lactating rats [see Data]. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women not to breastfeed during treatment with OFEV. Single-dose and repeat-dose OFEV plasma concentrations were similar in lactation rats and nursing infants. Concomitant administration of drugs that are highly protein bound may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary [see Warnings and Precautions].

Continued from previous page

group who received instruction about blood pressure and lifestyle modification, participants receiving the intervention saw significant reductions in systolic BP at 6 months (N Engl J Med. 2018 Apr 5;378:1291-391). From 6 months onward, participants in the intervention arm received fewer visits from pharmacists, though they still regularly visited the barbershop, where blood pressure was recorded. At the end of 12 months, systolic BP – at least 140 mm Hg at enrollment – dropped by 28.6 mm Hg from baseline in the intervention group to a mean 123.8 mm Hg. For those in the control group, the reduction in systolic BP was 7.2 mm Hg, to a mean 147.4 mm Hg. This 20.8-point difference between the two groups was highly statistically significant (P < .0001). These "new 12-month efficacy data are statistically indistinguishable from our previously reported 6-month data," wrote Ciantal Blyer, PharmD, a clinical pharmacist at Cedars-Sinai Medical Center, Los Angeles, and her coauthors. Diastolic BP, a secondary outcome measure, fell in the intervention group by 14.5 mm Hg more than in the active controls. In the intervention arm, 68% of participants reached the prespecified goal blood pressure of less than 130/80 mm Hg, while just 11% of the control group hit this target, a significant difference. No trial participants experienced treatment-related adverse events or deaths during the 6-month extension phase. Compared with men in the active control arm, those receiving the intervention were on a greater number of antihypertensive classes per regimen. Also, patients receiving the intervention were more likely to receive first-line drugs as add-on therapy. At the end of the 12-month period, all participants in the intensive arm were on antihypertensives, up from 37% at baseline. For the control group, antihypertensive medication use went from 53% at baseline to 65% at 6 months (P < .0001).

The intervention group saw their PCP much more than did the control group during the study; there was no difference in PCP visit frequency at baseline. This suggests that the pharmacist intervention did not interfere with the patient-PCP relationship, and perhaps influenced the increase in PCP visits," noted Dr. Blyer and her colleagues. The investigators noted that the pharmacists’ ability to begin, titrate, and change hypertension medication under a collaborative agreement with physicians was an essential part of the program’s initial and continued success. “Perhaps the most critical first step toward widespread dissemination of our model is the expansion of collaborative practice between pharmacists and physicians, or the elimination of the requirement altogether (as in Canada and the UK),” wrote Dr. Blyer and her coauthors.

The study was funded by the National Institutes of Health, the California Endowment, the Lincy Foundation, the Harriet and Steven Nichols Foundation, the Smidt Heart Institute, and the Division of Community Relations and Development at Cedars-Sinai Medical Center, Los Angeles. One coauthor reported being a consultant for Recor Medical; other authors reported that they had no disclosures.
**Phone app diagnoses STEMI nearly as well as ECG**

**BY BRUCE JANCIN**  
MDedge News

CHICAGO – A novel smartphone app performed nearly as well as a standard 12-lead ECG for diagnosis of ST-segment elevation MI (STEMI) in patients presenting with chest pain in ST LEUIS, an international, multicenter study.

“This study demonstrates that a 12-lead-equivalent ECG obtained using a smartphone coupled with a software application and inexpensive two-wire attachment can identify STEMI versus non-STEMI with an excellent correlation to a traditional 12-lead ECG. This technology holds substantial promise to improve outcomes in STEMI by enabling more rapid diagnosis and treatment anywhere in the world for inexpensive cost,” J. Brent Muhlestein, MD, said while presenting the ST LEUIS results at the American Heart Association scientific sessions.

This technology could provide a long-sought breakthrough in overcoming patient denial and motivating hard-headed individuals with a life-threatening MI to get to the hospital more quickly after symptom onset, instead of initially shrugging off the matter as indigestion. If individuals can use their handy cell phone or smartwatch to quickly obtain an ECG that shows they’re having a STEMI, they’re going to seek medical attention much sooner, with resultant greater salvage of heart muscle, noted Dr. Muhlestein of Intermountain Healthcare in Salt Lake City.

ST LEUIS tested whether a smartphone ECG app developed by AliveCor can accurately diagnose STEMI in patients with chest pain. The study, which took place at Intermountain Medical Center and a handful of other sites associated with the Duke University Cooperative Cardiovascular Society, included 204 patients who presented to EDs with chest pain. They simultaneously received both a standard 12-lead ECG and an ECG obtained using the AliveCor smartphone app. The matched ECG pairs were evaluated separately, both quantitatively and qualitatively, by a blinded panel of experienced cardiologists and classified as STEMI, left bundle branch block, non-STEMI, or uninterpretable. The study population included 92 patients with chest pain and activation of a STEMI protocol and 112 who came through the ED chest pain protocol.

Side-by-side ECG comparisons weren’t attempted in 14 pairs deemed not interpretable. In 13 cases this was because of technical problems with the smartphone ECG, and in the 14th because of ventricular pacing in the standard 12-lead ECG. STEMI was diagnosed in 22.5% of the study population by 12-lead ECG and in 29.4% by smartphone app. The discrepancy was explained by small voltage differences in the ST-segment elevation which met criteria for STEMI by smartphone but not standard 12-lead ECG in 15 cases.

“It appears that the ST elevation was a little bit more obvious in the smartphone ECG,” Dr. Muhlestein observed.

Left bundle branch block was identified in 5.4% of patients by both methods.

The key performance numbers: The smartphone ECG had a sensitivity of 89%, specificity of 84%, positive predictive value of 70%, and negative predictive value of 95% for diagnosis of STEMI or left bundle branch block. The positive predictive value was diminished by the increased likelihood that the smartphone would call STEMI in discordant cases.

Dr. Muhlestein said that, despite the AliveCor device’s very good correlation with the standard 12-lead ECG, the system needs further tweaking.

“I’m sure smart engineers can make a much more simple, really user-friendly device now that we know it’s actually feasible,” he said.

Dr. Muhlestein had no disclosures regarding the study, which was sponsored by the participating medical institutions.

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**Invasive strategy raised bleeding risk in frail AMI patients**

**BY ANDREW D. BOWSER**  
MDedge News

Frail older patients with acute myocardial infarction (AMI) may be at increased bleeding risk if managed with an invasive strategy, results of a large U.S. registry study suggest.

The increased bleeding risk was seen among frail older AMI patients who underwent cardiac catheterization, but it was not seen in those treated with more conservative medical management, according to study results.

That finding highlights the conundrum with invasive management strategies for frail patients with AMI, wrote John A. Dodson, MD, of New York University.

“Awareness of vulnerability and greater utilization of evidence-based strategies to reduce bleeding, including radial access and properly dose-adjusted anticoagulant therapies, may mitigate some bleeding events,” they wrote in JACC: Cardiovascular Interventions.

Results of this study, the first large U.S. registry analysis evaluating in-hospital bleeding risk in frail older adults with AMI, confirm findings from several previous small cohort studies linking frailty in AMI patients to in-hospital bleeding, investigators reported.

The analysis included a total of 129,330 AMI patients in the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry who were aged at least 65 years in 2015 or 2016. About one in six of these older patients were frail, as defined by a composite score based on impaired walking, cognition, and activities of daily living, investigators reported.

The bleeding rate was significantly higher among frail patients undergoing cardiac catheterization, at 9.4% for patients rated as having vulnerable/mild frailty and 9.9% for patients with moderate to severe frailty (P less than.001), compared with fit/well patients, whose rate was 6.5%, investigators wrote. By contrast, there was no significant difference in bleeding rates for frail versus nonfrail patients managed conservatively, they said.

After adjusting for bleeding risk factors, frailty was independently associated with increased risk of bleeding, compared with fit/well status, with odds ratios of 1.33 for vulnerable/mild frailty and 1.40 for moderate to severe frailty. Again, no association was found between frailty and bleeding risk in patients managed conservatively, according to investigators.

Frail patients in the ACTION registry were more often older and female and less likely to undergo cardiac catheterization when compared with fit or well patients, they added in the report.

Dr. Dodson reported support from the National Institutes of Health/National Institute on Aging and from the American Heart Association. Study coauthors provided disclosures related to Bayer, Janssen, Abbott Vascular, Jarvik Heart, LifeCuff Technologies, and Ancora Heart.

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**VIEW ON THE NEWS**

G. Hossein Almassi, MD, FCCP, comments: This is yet another study supporting the promise and the applicability of smart phone technology in early diagnosis and management of STEMI.
Combined risk factors raise coronary event rates

BY RICHARD MARK KIRKNER
MDedge News

CHICAGO – Individuals with both elevated lipoprotein(a) levels and a family history of coronary heart disease have a considerably higher long-term risk of atherosclerotic cardiovascular disease than those with one risk factor alone, according to results from a large clinical study presented at the American Heart Association scientific sessions.

“Elevated lipoprotein(a) levels or a positive family history of coronary heart disease each is independently associated with cardiovascular disease risk,” said Anurag Mehta, MD, of Emory University School of Medicine, Atlanta. “This study showed that the presence of both an elevated Lp(a) level and a positive family history has an additive joint association with long-term cardiovascular risk.”

Dr. Mehta reported on an analysis of 12,149 individuals participating in the Atherosclerosis Risk in Communities (ARIC) study. All study participants were free of cardiovascular disease at the time of enrollment. The researchers measured Lp(a) levels and ascertained family history by self-report. Forty-four percent of the study participants had a family history of coronary heart disease (CHD), and 23% were black. Black participants had a significantly higher average plasma Lp(a) concentration than white persons, at 16.7 mg/dL vs. 5.7 mg/dL. However, plasma Lp(a) levels between participants with either a positive or a negative family history of CHD were similar on average, 7.6 mg/dL and 7.8 mg/dL, respectively.

The study pooled black and white ARIC participants by race-specific Lp(a) levels (quintiles) and stratified them into four different groups: 1. positive family history and an elevated race-specific Lp(a) level (quintile 5); 2. positive family history and nonelevated race-specific Lp(a) level (quintiles 1–4); 3. negative family history and elevated race-specific Lp(a) level (quintile 1–4); 3. negative family history and nonelevated race-specific Lp(a) level. “There was an increase in the proportion of participants with a family history of CHD across race-specific Lp(a) quintiles, highlighting the fact that family history is associated with race-specific Lp(a) levels,” Dr. Mehta said.

“The highest ASCVD incidence was noted among participants with an elevated Lp(a) level as well as a positive family history.” Among those patients, the cumulative incidence of ASCVD events was nearly 25%, compared with 22% for those with a positive family history and nonelevated Lp(a) levels (group 2) or those with a negative family history but elevated Lp(a) levels (group 3), and 18% for those with negative family history and nonelevated Lp(a) levels.

Results for the cumulative incidence of coronary events trended similarly.

Composite screening tools increase PAH detection

BY TED BOSWORTH
MDedge News

In patients at risk for pulmonary arterial hypertension (PAH) due to a connective tissue disease, composite novel screening methods are improving early detection when employed in the context of traditional tools, such as transthoracic echocardiography (TTE), according to a systematic review of studies published over the last 5 years.

The review was conducted to prepare for a guideline update, according to the authors of this recently published summary in Seminars in Arthritis and Rheumatism.

In a literature review for 2012–2015, the authors evaluated whether new tools or strategies have improved PAH screening in patients with connective tissue disease since the last review was undertaken (Semin Arthritis Rheum 2014;43:536-41).

The latest review found that, although TTE and pulmonary function tests (PFT) remain a mainstay of screening, there is growing evidence that composite measures, such as the DETECT and ASIG algorithms, add sensitivity and specificity, compared with guidelines that rely on TTE and PFT alone.

After a literature search, the systematic review included 16 cohort studies and 6 case-control studies. Most of these evaluated PAH screening strategies for patients with systemic sclerosis specifically despite the potential for other connective tissue disease etiologies to lead to PAH.

“We need more longitudinal observational studies to develop and validate screening algorithms for non–systemic sclerosis connective tissue diseases,” stated the authors, led by senior investigator Dinesh Khanna, MD, medical director of ambulatory and chronic disease in the University of Michigan’s Office of Research, Ann Arbor.

Relative to screening primarily based on TTE and PFT as advocated in 2009 joint guidelines from the European Society of Cardiology and the European Respiratory Society (ESC/ERS), the preponderance of data supported the addition of DIRECT and ASIG algorithms to improve the sensitivity and specificity of traditional screening and diagnostic tools, according to the data reviewed.

Several of the studies evaluating DETECT and ASIG compared their sensitivities and specificities to the screening strategy recommended in the 2009 ESC/ERS guidelines be-
TRED-HF: Despite recovery, dilated cardiomyopathy returns after halting HF drugs

BY BRUCE JANCIN

CHICAGO – Phased withdrawal of guideline-directed medical therapy in patients who seemed to have recovered from dilated cardiomyopathy resulted in relapses in 40% of patients within 6 months in the TRED-HF trial.

The clinical implications of this small pilot randomized trial are clear: “Withdrawal of therapy should not usually be attempted, at least until we can predict who’s going to relapse and who’s not,” Dr. Brian P. Halliday, MD, PhD, said at the American Heart Association scientific sessions.

“Improvement in function represents remission rather than permanent recovery for many patients,” added Dr. Halliday of Imperial College London.

The study was performed to address a question that arises with increasing frequency in clinical practice as a result of the impressive advances in heart failure therapy in recent years, he said. “Patients frequently come to us in clinic and ask us, ‘Do I need to continue to take these medications forever?’ They’re frequently young, and they want to know if they really need to be on therapy for 40 or 50 years of medication. Some are concerned about side effects, others are interested in pregnancy, and then there is the financial cost.”

Simultaneously published in The Lancet, TRED-HF was a single-center, open-label study of 51 patients who had prior dilated cardiomyopathy (DCM) and a median left ventricular ejection fraction (LVEF) of 25% at the time of diagnosis 4.9 years earlier and who subsequently recovered in response to therapy. That is, they became symptom free with an LVEF greater than 50%, a normal left ventricular end-diastolic volume index, and a reassuringly low median N-terminal pro b-type natriuretic peptide (NP-pro-BNP) level of 72 ng/L.

For the study, 25 patients were randomized to phased withdrawal of their heart failure drugs over a 16-week period: First they reduced or stopped loop diuretics, then mineralocorticoid antagonists, then beta-blockers, and finally their ACE inhibitor or angiotensin receptor blocker. The other 26 participants continued therapy during the first 6 months of the study, then 25 of the 26 crossed over to phased withdrawal.

The primary endpoint was relapse of DCM within 6 months of the start of the study. Relapse was defined as either a drop in LVEF of more than 10% to a level below 50%, at least a doubling of NT-pro-BNP to greater than 400 ng/L, clinical evidence of heart failure, or a greater than 10% increase in LV end-diastolic volume as assessed by cardiac MRI.

Results presented

During the first half of the study, 11 of 25 patients (44%) relapsed during or after medication withdrawal. None of the controls relapsed. In the crossover phase, 9 of 25 patients (35%) relapsed in response to treatment withdrawal. Of the 20 patients who relapsed, 13 did so within 16 weeks of beginning medication withdrawal. Indeed, most patients relapsed within 8 weeks of their last medication. Ten of the twenty fulfilled multiple criteria for relapse.

Medication withdrawal was accompanied not only by a mean 9.5% reduction in LVEF, compared with baseline, but by a 15.4-bpm rise in heart rate, a 7.0-mm Hg increase in diastolic blood pressure, and 5.1-point deterioration in Kansas City Cardiomyopathy Questionnaire scores, demonstrating that what happened off treatment was true DCM recurrence and not simply an imaging artifact.

Everyone who relapsed immediately restarted treatment. At their next follow-up visit, all were once again asymptomatic, and 17 of the 20 (85%) had an LVEF greater than 50%. Two of the other three had an LVEF of 45%-50%, and the other had an LVEF of 43%.

“So they did seem to recover when they went back on medication,” Dr. Halliday observed.

Experts react

Designated discussant Jane E. Wilcox, MD, commented, “Currently, in 2018, we have no true signature of recovery. These patients are indeed in cardiac remission and have an indefinite indication for continuing their evidence-based medical therapy without interruption.”

“The clinical implication here is, I think, we should TRED-likely,” quipped Dr. Wilcox of Northwestern University in Chicago.

Her own research indicates that even patients who have recovered their LVEF and no longer seem to have a heart failure phenotype still have an abnormal myocardial substrate as evidenced by persistent dysfunctional cardiac mechanics on echocardiography. But she remains optimistic.

“I don’t think [TRED-HF] squelches the future of myocardial recovery. I think it actually invigorates the field for an assessment of genomics, proteomics, and metabolomics looking for that true signature of cardiac recovery,” she said.

Donald Lloyd-Jones, MD, who chaired a press conference where Dr. Halliday presented the TRED-HF results, said “I really want to commend the investigators for taking on what, on its face, might be an ethically challenging question by taking treatment away when we don’t know what the answer is likely to be. But they really checked all the boxes to make sure this was done in a very safe and monitored way, so that even though the outcome was what it turned out to be, the harm to patients was minimalized. Dr. Lloyd-Jones is professor and chair of the department of preventive medicine and director of the Northwestern University Clinical and Translational Sciences Institute, Chicago.

Dr. Halliday reported no disclosures regarding the study, funded by the British Heart Foundation.


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.

**FASENRA DEMONSTRATED POWERFUL EFFICACY ACROSS EXACERBATIONS, LUNG FUNCTION, AND OCS USE**

- **51% Reduction in AER**
- **75% Reduction in Median OCS Dose**
- **398 mL Increase in FEV**

(0.74) compared to placebo + SOC (1.52) in Trial 1 (48 weeks)

FASENRA (n=267) Placebo (n=267) (P<0.001)2

FASENRA (n=73) Placebo (n=75) (P<0.001)4

Compared to 25% reduction with placebo + SOC in Trial 3 (28 weeks)

FASENRA (n=264) Placebo (n=261) (P<0.0006)2

Compared to 239 mL with placebo + SOC in Trial 1 (48 weeks)

**Trial 2** improvement in FEV1 for FASENRA + SOC (330 mL; n=238) was 116 mL greater than placebo + SOC (215 mL; n=244), with FASENRA + SOC showing a 19% improvement from mean baseline FEV1 of 1.76 L (P=0.010).1,3

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.

**FASENRA**

(0.73; n=239) reduced AER by 28% compared to placebo + SOC (1.01; n=248) in Trial 2 (56 weeks) (P=0.019)3

FASENRA (n=73) Placebo (n=75) (P<0.001)4

**398 mL Increase in FEV**

(0.74) compared to placebo + SOC (1.52) in Trial 1 (48 weeks)

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FASENRA (n=264) Placebo (n=261) (P<0.0006)2

**MAKE FASENRA YOUR FIRST CHOICE RESPIRATORY BIOLOGIC**

**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.
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 versus placebo in patients with blood eosinophil counts of ≥300 cells/μL on high-dose ICS and LABA. Exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, temporary increase in a stable OCS background dose for ≥3 days, emergency/urgent care visit because of asthma that needed systemic corticosteroids, or inpatient hospital stay of ≥24 hours because of asthma. Key secondary endpoints were pre-bronchodilator FEV₁, and total asthma symptom score at Week 48 (Trial 1) and Week 56 (Trial 2) in the same population.²,³

TRIAL 3
A 28-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter OCS reduction study comparing the efficacy and safety of FASENRA (30 mg SC) Q4W for the first 3 doses, then Q8W thereafter; benralizumab (30 mg SC) Q4W, and placebo (SC) Q4W. A total of 220 adult (18-75 years old) patients with severe asthma on high-dose ICS plus LABA and daily OCS (7.5 to 40 mg/day), blood eosinophil counts of ≥150 cells/μL, and a history of ≥1 exacerbation in the previous year were included. The primary endpoint was the median percent reduction from baseline in the final daily OCS dose while maintaining asthma control.⁴


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 ADDITIONAL IMPORTANT SAFETY INFORMATION ON PREVIOUS PAGE AND 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.
Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred at any time during treatment with 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

Acute asthma symptoms or deteriorating disease may occur in patients who have pre-existing asthma. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

Reduction of Corticosteroid Dose

Do not decrease systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. A gradual and prolonged withdrawal is recommended. Reducing corticosteroid dose too rapidly has resulted in the exacerbation of asthma and/or exacerbations of pre-existing eosinophilic conditions. Inform patients that FASENRA should be administered at the recommended dose of 30 mg administered once every 4 weeks for at least 1 year. FASENRA is for subcutaneous use only.

Parasitic (Helminth) Infection

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Smoke-free policies improve public health, lower BP

BY STEVE CIMINO
MDedge News

A
reas that have adopted smoke-free policies in their restaurants, bars, and workplaces have seen a corresponding drop in systolic blood pressure, according to data from the Coronary Artery Risk Development in Young Adults (CARDIA) study.

"Among a geographically diverse cohort of black and white nonsmoking adults followed for 15 years, we found that participants living in areas with smoke-free policies in restaurants, bars, and workplaces had lower systolic blood pressure at the end of follow-up, compared with participants living in areas without smoke-free policies," wrote Stephanie L. Mayne, PhD, of the department of preventive medicine at Northwestern University, Chicago, and her coauthors in the Journal of the American Heart Association.

The study analyzed data from 2,606 CARDIA participants, all of whom enrolled in 1985-1986 and underwent follow-up exams after 2, 5, 7, 10, 15, 20, 25, and 30 years. Smoke-free policies were obtained from the American Non-Smokers’ Rights Foundation’s Local Ordinance Database and linked to participants based on their census tract and examination date. Systolic and diastolic blood pressure (SBP, DBP), along with physical activity and dietary quality, were measured at each examination.

By year 25, participants in areas with smoke-free restaurants had SBP values that were 1.14 mm Hg lower than participants who lived in areas with smoke-friendly restaurants (95% confidence interval, 2.15-0.12). Participants in areas with smoke-free bars returned similar results, with a SBP difference of 1.52 mm Hg (95% CI, 2.48-0.57). The data were less conclusive for DBP, though CARDIA indicated that SBP was more associated with cardiovascular disease risk than DBP and "even small reductions in SBP may result in meaningful reductions in CVD risk."

The coauthors shared the study’s potential limitations, including an inability to control for antismoking campaigns and the possibility that participants did not report any infrequent smoking habits. They also noted, "Strengths of this study include use of data from a large, geographically diverse cohort with 15 years of follow-up, and use of fixed-effects models to tightly control for both measured and unmeasured time-invariant characteristics of participants. In addition, previous associations between smoke-free policies and reduced risk of hospitalization for CVD, noting the relation and suggesting “BP reduction as a potential mechanism through which smoke-free policies may reduce rates of CVD at the population level.”

This study was supported by the National Heart, Lung, and Blood Institute, in collaboration with the University of Alabama at Birmingham, Northwestern University, the University of Minnesota, Kaiser Foundation Research Institute, and Johns Hopkins University School of Medicine. It was partially supported by the Intramural Research Program of the National Institute on Aging. No conflicts of interest were reported.

Rates, costs, mortality of RA-related interstitial lung disease analyzed in new study

BY STEVE CIMINO
MDedge News

Interstitial lung disease (ILD) is becoming more prevalent in patients with rheumatoid arthritis (RA) while shortening survival and leading to substantial health care costs, according to a retrospective study of RA-ILD prevalence, incidence, costs, and mortality.

"To our knowledge, this is the first study to describe the incidence and prevalence of RA-ILD among the general population and to estimate costs among U.S. patients with RA-ILD," wrote lead author Karina Raimundo, principal health economist at Genentech, and her coauthors in the Journal of Rheumatology.

The study reviewed data from the Truven Health MarketScan Commercial and Medicare Supplemental health insurance databases, along with linking a subset of patients to the Social Security Administration Death Index to determine mortality.

From 2004 to 2013, with the number of patients ranging from 892 to 3,232 per year, yearly prevalence estimates ranged from 3.2 (95% confidence interval, 3.0-3.4) to 6.0 (95% CI, 5.7-6.2) RA-ILD cases per 100,000 people. Yearly incidence ranged from 2.7 (95% CI, 2.5-2.9) to 3.8 (95% CI, 3.5-4.0) cases per 100,000 people.

While incidence was relatively stable, prevalence increased over the 10-year period. The authors noted that increased prevalence suggests improved survival of RA-ILD patients but were unable to definitively state why, with explanations ranging from more effective therapies to earlier diagnosis of the disease. "Our data do not allow more in-depth evaluation of this issue, and it merits further analysis.”

In addition, they found that average yearly costs across all study years ranged from $40,941 (standard deviation, $55,682) to $51,849 (SD, $77,125), with the main cost drivers being inpatient admissions, outpatient services, and outpatient pharmacy.

By the 5-year mark of first diagnosis, 35.9% of RA-ILD patients who could be linked to the SSDI had died; those patients – with a mean age of 65 years – also had a median survival of 7.8 years (95% CI, 7.1-8.3). Generally, a 65-year-old person in the United States would be expected to live for 19 more years.

The authors acknowledged the study’s limitations, including reliance on administrative claims data, subsequent misclassification of RA-ILD status, a lack of information on cause of death, and an underestimation of mortality caused by the inability to link all patients to the Social Security Administration Death Index.

The study was funded by Genentech and Hoffmann–La Roche. No other conflicts of interest were reported.

Seeking the wisdom of the CHEST crowd

BY CLAYTON T. COWL, MD, MS, FCCP

The wisdom of the crowd is the collective opinion of a group of individuals rather than that of a single expert. At CHEST, the makeup of our membership is diverse and energetic, and it comprises individuals with unique expertise who not only serve as faculty but who are also eager for opportunities themselves to learn. That collective wisdom, leveraged over the entire membership, is what the leadership of CHEST will be listening to this year as we create new educational products and continuously improve the annual meeting and other courses held throughout the year. From broad-based general overviews such as CHEST’s board reviews, to more specific courses such as training in bedside ultrasound or ventilator management, each is geared to make all of us better clinicians who will recognize and provide the latest and most effective treatments for our patients.

If you had the opportunity to attend my opening address at the CHEST annual meeting in San Antonio in October, you heard me talk about the innate wisdom of “the crowd.” We all have various “crowds” in our lives – our work colleagues, families, and relationships in professional societies.

I reminded the audience that if we take the time to listen to each of these “crowds,” they usually know the answers. In the coming year, we, as a leadership team for CHEST, will be focusing on being better listeners and utilizing “our crowd” of members to better connect in order to develop educational products that will train clinicians, educators, and researchers in the very latest and most effective care in pulmonary, critical care, and sleep medicine.

Here are just a few initiatives planned this year that have come in response to member comments and suggestions:

• Digital Strategy Task Force – This multidisciplinary group, composed of both volunteer members and association staff, has been assigned to evaluate the user experience associated with existing CHEST content delivery platforms and highlight opportunities for improvements. In this effort, they will identify trends that will enable the organization to better execute on the digital-dependent strategies in the organization’s strategic plan in a successful way. The group will be making recommendations to the Board of Regents that will include timelines, goals, and specific objectives, define organizational voice and brand messaging present on web and other platforms, and create specific metrics to measure the user experience on an ongoing basis.

• Optimizing Board Review Courses – CHEST will be looking at ways to present some content on digital platforms that are difficult to teach in a classic didactic format. Topics such as acid-base disturbances and biostatistics are more effectively presented using a digital, problem-based format. Efforts will be made to shorten board review courses slightly without compromising quality or jeopardizing coverage of content and to incorporate succinct bulleted summaries of each topic covered. In addition, plans are in place to create new courses that will train learners the techniques for passing the new “low stakes” board examination offered by the ABIM.

• Making membership more affordable for international colleagues – New discounted membership rates have been launched to allow international members to obtain the “Enhanced” level of membership to be eligible for fellowship in the association (ie, the FCCP designation). Volume discounts have been introduced for regional chapters and organizations to allow health-care team members from around the world to join CHEST in conjunction with their local society at a fraction of the cost of a single member rate.

• Patient education modules from the CHEST Foundation – A variety of patient education modules are now available to providers, as well as to the general public for information on a wide array of topics – from correct use of inhalers to state-of-the-art therapies for COPD or lung cancer.

• Improved opportunities for member participation – From improved instructions for joining a CHEST NetWork to specific orientation instructions for new members of the Board of Regents, improved communications have become available to help members become better acquainted with the framework of the organization and allow them to become more effective once they begin new leadership roles.

• Embracing innovation – This year, the organization will launch CHEST Inspiration, a program that involves development of an environmental scan to be shared with our members regarding how CHEST can be a differentiator in an environment where quality education is becoming more accessible and, as a result, more competitive. As part of this initiative, CHEST will plan to host a series of focus group sessions to act on the environmental scan and will also roll out an innovation competition at the 2019 annual meeting in New Orleans in October.

• Expanded international strategy – CHEST is responding to the requests from member groups in countries within Asia, Europe, Latin America, and the Middle East to hold a CHEST Congress each spring to bring the best of the CHEST annual meeting to our colleagues from around the world who may not be able to travel to the meeting held in the United States, as well as a more intimate board review-like meeting each summer in various regions of the world. For example, this year, the College will host a CHEST Congress in Bangkok, Thailand, April 10-12, and a regional meeting in Athens, Greece, June 27-29.

We are committed to improving communication with our members and encouraging innovation regardless of their prior participation levels. CHEST will continue to bring its brand of education focused on more hands-on learning and team-based knowledge using simulation, serious gaming, and artificial intelligence in the years ahead. CHEST leaders have begun to be active on social media, and we will be introducing new platforms for all members to better understand what is happening from a leadership perspective. Together, we will be able to harness the collective wisdom of our talented and innovative members in order to make a lasting difference for our patients.

Explore the Moderate to Severe Asthma Center of Excellence

Visit Now | bit.ly/AsthmaCenterOfExcellence

Engage with CHEST and Medscape as they partner on the Moderate to Severe Asthma Center of Excellence, designed to support physicians in addressing the challenges of diagnosing and treating moderate to severe asthma.

Rotating content will include articles, videos, commentary, and news on diagnostic, therapeutic, and prevention strategies, including the latest research and breakthroughs.

New content will be added often, so check back for updates.

JUST ADDED

• Asthma Emergencies: A Guide to Treating Potentially Life-Threatening Exacerbations [video]
• Biology of Asthma and Biologics: A Primer
• Transitioning Adolescents With Asthma to the Adult Model of Care [video]

Other current topics include:

• Asthma Redefined: Managing Multiple Diseases: Unmasking the Culprit
• Bronchial Thermoplasty: A Viable Option for Severe Asthma
• Diagnosing Severe Asthma: Not as Easy as it Sounds

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SLEEP STRATEGIES

The emerging role of sleep in the development of Alzheimer disease

BY RAMAN K. MALHOTRA, MD; AND BRENDAN P. LUCEY, MD, MSCI

More than 5 million Americans are living with Alzheimer disease (AD), making this the leading cause of dementia in the United States. This number is projected to nearly triple to 14 million people by 2060 (Matthews KA, et al. Alzheimers Dement. 2018 Sep 17. doi: 10.1016/j.jalz.2018.06.3063. [Epub ahead of print]).

Experts predict estimated costs related to AD to be more than $500 billion annually starting in 2040 (Hurd MD, et al. N Engl J Med. 2013;368[14]:1326). AD is a neurodegenerative disorder characterized by gradual, progressive decline in memory along with other cognitive functions, eventually leading to impairment in activities of daily living. Most current treatments for AD are symptomatic and only minimally slow progression of disease. The increasing prevalence, overwhelming costs to society, and the absence of a cure for AD have created an impending national health crisis.

As the dementia progresses, sleep also tends to worsen. Currently, clinicians improve sleep in patients already diagnosed with AD through diagnosis and treatment of sleep disorders, such as insomnia and sleep apnea, to improve overall functioning and quality of life. Treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) in patients diagnosed with AD has shown to improve cognition and other neurocognitive measures (Ancoli-Israel S, et al. J Am Geriatr Soc. 2008;56[11]:2076).

However, there is mounting interest in evaluating how poor sleep could lead to future development of AD or serve as a marker for AD disease in preclinical or asymptomatic populations. Sleep symptoms can be a precursor of other neurological diseases; for example, dream enactment (REM sleep behavior disorder) can precede onset of neurodegenerative disease (Parkinson disease) by decades. Increasing evidence suggests that sleep disruption seen in early or even preclinical AD contributes to its onset and progression. In response to this growing body of research, in June 2018, the American Academy of Sleep Medicine (AASM) issued a health advisory to patients and providers to consider early intervention to ensure sufficient sleep and to treat sleep disorders to assist prevention or delaying onset of AD.

**Poor sleep as a risk factor for Alzheimer disease**

Epidemiologic studies (both cross-sectional and prospective studies) have demonstrated that fragmented sleep in cognitively normal individuals is a risk factor for the future development of symptomatic AD (Bubu OM, et al. Sleep. 2017[Jan];1:40). The pathogenesis of AD includes abnormal accumulation of the protein, amyloid-β (Aβ), in the brain as insoluble...
extracellular plaques followed by intracellular aggregation of tau, neuronal loss, and cognitive dysfunction. Aβ deposition in the brain begins approximately 15 to 20 years before the onset of cognitive impairment and serves as an early biomarker of AD. Accumulation of Aβ results from imbalance between production and clearance of the protein from the central nervous system.

Numerous studies have demonstrated that people with disrupted sleep may show early evidence of AD, such as Aβ deposition compared with healthy sleepers. In one study, cognitively normal people with Aβ plaque disease had worse sleep efficiency and increased nap frequency measured by actigraphy as compared with cognitively normal individuals without Aβ plaques (Ju YE, et al. JAMA Neurol. 2013 [May];70[5]:587). Further, a recent study found that self-reported daytime sleepiness was associated with longitudinal increases in Aβ deposition (Carvalho DZ, et al. JAMA Neurol. 2018 [Jun];75[6]:672).

**Possible mechanisms**

Possible mechanisms have been suggested to explain how poor sleep may lead to AD. Over the past 10 years, sleep deprivation was found to increase Aβ concentrations in both a mouse model (Kang JE, et al. Science. 2009;326:1005) and humans, most likely through increased production and/or release of Aβ (Lucey BP, et al. Ann Neurol. 2018;83[1]:197). Sleep also appears to increase clearance of proteins and other molecules via bulk fluid flow (“glymphatic” clearance). Glymphatic clearance may enable the removal of intersectal toxic proteins, such as Aβ, through a dynamic interaction between the cerebrospinal fluid and the interstitial fluid, where astrocytes facilitate extracellular fluid transit through the brain during sleep (Xie L, et al. Science. 2013;342:373). Since Aβ deposition in the brain is concentration-dependent, higher Aβ levels from sleep disturbance could lead to greater deposition in the brain.

**Circadian rhythm and Alzheimer disease**

Another mechanism linking sleep to the pathogenesis of AD includes disruption of the circadian rhythm, which is commonly seen in patients with AD. Studies have linked populations who suffer from circadian rhythm disorders to higher rates of dementia (Tranah GI, et al. Ann Neurol. 2011;70[5]:722). Circadian disruption may predispose the brain to neurodegenerative conditions by altering immune function, disrupting endocrine function, increasing inflammation and oxidative stress, or affecting neurogenesis (in specific areas such as the hippocampus). Thus, inadequate sleep could prime the brain for neurodegeneration by multiple pathways.

**Obstructive sleep apnea and Alzheimer disease**

Sleep disruption and chronic intermittent hypoxia secondary to untreated OSA has also been associated with AD. Numerous studies have shown that sleep-disordered breathing is associated with AD risk and that AD patients have higher rates of OSA. For instance, a study in older women found that moderate and severe sleep-disordered breathing was associated with an increased risk of future cognitive impairment and dementia (Yaffe K, et al. JAMA. 2011 [Aug];306[6]:613). In addition to sleep disruption from sleep apnea affecting Aβ as detailed above, hypoxia from sleep apnea may also alter risk of future AD.

**Future directions**

Studies support a clear bidirectional relationship between AD and sleep. As researchers continue to investigate sleep as a marker for AD, others are exploring the implications of using sleep interventions to prevent and/or delay the onset of AD. Patients with poor and disrupted sleep may be the ideal candidates for sleep interventions to lower the risk of AD, such as treating OSA with CPAP therapy or insomnia with hypnotic medication or cognitive behavioral therapy. These therapies are already well-studied and approved for human use, allowing for rapid translation to future intervention trials.

Dr. Malhotra is Associate Professor, Sleep Medicine Section; and Dr. Lucey is Assistant Professor, Director-Sleep Medicine Section; Department of Neurology, Washington University School of Medicine, St. Louis, Missouri.

**NIH funds project of CHEST Foundation grant winner Drew Harris, MD**

While in San Antonio for CHEST 2018, CHEST Foundation Research Grant in Asthma, Drew Harris, MD, to learn about the impact of winning a CHEST Foundation Research grant had on his community and career. Dr. Harris’ project created a medical-legal partnership to target many of the social determinants of asthma and help address them beyond the typical scope a provider can offer in a traditional visit.

“Currently, we have a full-time lawyer, two social workers, and people in Public Health Sciences program, as well as law students at The University of Virginia (UVA) all working together to address the needs of the community,” Harris stated. “Public health students conduct asthma screenings in any of the four clinics we partner with within the UVA system and bring their findings to the larger group. From there, we figure out how to best intervene for these people and connect them with our lawyer if there are housing or workplace discrimination concerns.”

Dr. Harris recently received NIH funding for his approach and has since expanded this medical-legal partnership at the University of Virginia. “The grant I received last year from the CHEST Foundation funded a pilot version of my project that I then was able to share with a larger audience and ultimately secure federal funding for,” Dr. Harris shared.

“The NIH grant was awarded through the lens of implementation science. We know what works in asthma medication and environmental and social factors that help improve patients’ lives. But we do a poor job on actually DOING it. Our project addresses barriers to fixing these social needs and brings a team together to help fix these other problems that are hard for just a medical provider to address.” Dr. Harris continued, “Social needs and determinants of health are starting to receive more attention in pulmonary medicine, so we are really hitting the ground at the right time. Everyone understands that these are important determinants of health, but they lack the tools to help improve patients’ lives. We are creating those.”

Your donations support clinical research projects like this grant for Dr. Harris. Please consider making a donation to support next year’s grants. https://foundation.chestnet.org/donate/.

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Pneumonia, PIONEER-HF, malignant pleural effusion

The recent PIONEER-HF trial now provides evidence to support safety of careful initiation of sacubitril-valsartan for hospitalized patients with and without prior exposure to RAS.

Cardiovascular Medicine and Surgery
PIONEER-HF trial: Changing practice in patients hospitalized for heart failure

Renin-angiotensin system (RAS) inhibition forms a pivotal part of guideline-recommended therapy for patients with heart failure with reduced ejection fraction (HFrEF).\(^1\) Inhibition of the neutral endopeptidase neprilysin increases levels of several vasoactive peptides that inhibit progression of HF.\(^2\) The randomized PARADIGM HF trial compared sacubitril/valsartan (angiotensin receptor neprilysin inhibition, ARNI) to enalapril in patients treated with ARNI; mortality and rehospitalization were decreased significantly, as well.\(^3\) Importantly, patients had to be clinically stable and complete a sequential run-in period to be eligible for randomization. On this basis, the 2017 HF guideline update recommended transition from RAS inhibition to ARNI in trial-eligible patients.\(^4\)

The recent PIONEER-HF trial now provides important evidence to support safety of careful initiation of sacubitril-valsartan for hospitalized patients with and without prior exposure to RAS.\(^5\) Hemodynamically stable patients were started on a regimen of sacubitril-valsartan, usually at doses half of those used in PARADIGM-HF. The primary endpoint of a decrease in BNP levels was improved significantly with sacubitril-valsartan (ratio 0.71, CI 0.63–0.81; P < .001), and this translated into a significant decrease in the important patient-centered secondary endpoint of rehospitalization.\(^6\) ARNI are undertreated in eligible patients; complexity of outpatient drug initiation may contribute.\(^6\)

References

Clinical Research
Guidelines for the management of malignant pleural effusion

A multisociety multidisciplinary panel developed recommendations for management of malignant pleural effusions (MPE) by using the PICO (Population, Intervention, Comparator, and Outcomes) format. As per these guidelines, definitive therapy is aimed at minimizing symptoms, re-acumulation and repeated pleural interventions, and risk of interventions in asymptomatic MPE outweighing benefits. Pleural interventions were suggested for indications such as clinical staging, obtaining molecular markers, etc. (Tremblay A. J Bronchology Interv Pulmonol. 2007;14:98).

As per these guidelines, definitive therapy is aimed at minimizing symptoms, re-acumulation and repeated pleural interventions, and risk of interventions in asymptomatic MPE outweighing benefits. Outcomes of definitive therapy for symptomatic MPE are equivilocal between indwelling pleural catheter (IPC) and pleurodesis. IPC, which was restricted to un-expandable lungs in the previous guidelines, are now suggested for both expandable and un-expandable lungs (Feller-Kopman et al. Am J Respir Crit Care Med. 2018;198[7]:839).

Higher treatment failure rates with chemical pleurodesis, as well as low incidence rates of IPC-related cellulitis and pleural space infections, led the panel to suggest IPC for un-expanded lungs, treatment failures, and residual symptomatic loculated effusions. In patients with IPC-related infections, treatment of the infection rather than removal of the catheter was suggested unless in events where the infection failed to respond (Feller-Kopman et al. Am J Respir Crit Care Med. 2018;198[7]:839).

Bharat Bajantri, MD
Steering Committee Fellow-in-Training

Interprofessional Team
Difficult-to-control asthma, defined as: uncontrolled asthma despite use of maximum dose inhaled corticosteroids or chronic oral corticosteroids with daily asthma symptoms, frequent exacerbations, and/or hospitalization results in a substantial medical and financial

Continued on page 54
How does your choice of ICS/LABA stand up to a 24-hour world?

24-hour BREO for a 24-hour world

BREO is for adult patients with asthma uncontrolled on a long-term control medication (eg. ICS) or whose disease warrants an ICS/LABA (inhaled corticosteroid/long-acting beta_2-adrenergic agonist). BREO is NOT indicated for the relief of acute bronchospasm.

**Important Safety Information**

**CONTRAINDICATIONS**
- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intensive measures are required.
- BREO is contraindicated in patients with severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients.

**WARNINGS AND PRECAUTIONS**
- LABA monotherapy for asthma increases the risk of asthma-related death, and in pediatric and adolescent patients, available data also suggest an increased risk of asthma-related hospitalization. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.
- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used more frequently or at higher doses than recommended, or with another LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs, like LABA.
- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing after inhalation.

Please see additional Important Safety Information for BREO on the following pages.
Please see Brief Summary of Prescribing Information for BREO on the pages following this advertisement.
24-hour BREO for a 24-hour world

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

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

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

*In a randomized, double-blind (RDB) study of 1039 patients*† *symptomatic on a mid- to high-dose ICS, BREO 100/25 once daily (n=312) demonstrated a 108 mL improvement from baseline in weighted mean (wm) FEV₁ (0-24 hours) at the end of the 12-week treatment period vs fluticasone furoate (FF) 100 mcg once daily (n=288) (P<0.001). In an RDB, placebo-controlled study of 609 patients*‡ *symptomatic on a low- to mid-dose ICS, in a subset of patients, BREO 100/25 once daily (n=108) demonstrated a change from baseline in wm FEV₁ (0-24 hours) at the end of the 12-week treatment period vs FF 100 mcg once daily (n=106) of 116 mL [95% CI: –5, 236; P=0.06].

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

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

**Important Safety Information (cont’d)**

**WARNINGS AND PRECAUTIONS (cont’d)**

- Use caution in patients who use corticosteroids as they are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.

- Particular care is needed for patients transferred from systemic corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREO.

- Hypertension and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, discontinue BREO slowly.

- Caution should be exercised when considering the coadministration of BREO with long-acting ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and cardiovascular adverse effects may occur.

- If paradoxical bronchospasm occurs, discontinue BREO immediately and institute alternative therapy.

- Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO. Discontinue BREO if such reactions occur.

- Vilaanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If such effects occur, BREO may need to be discontinued. BREO should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**WARNINGS AND PRECAUTIONS (cont’d)**

- Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (eg, anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

- Glaucome, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

- Be alert to hypokalemia and hyperglycemia.

- Orally inhaled corticosteroids may reduce growth velocity in children and adolescents.

**ADVERSE REACTIONS**

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

Please see additional Important Safety Information for BREO on all pages.
Please see Brief Summary of Prescribing Information for BREO on the pages following this advertisement.
BREO has better formulary coverage nationally than Symbicort

Individual access may vary by geography and plan benefit design.
Source: Managed Markets Insight & Technology, LLC, database as of September 2018.

<table>
<thead>
<tr>
<th>4 Million</th>
<th>2 Million</th>
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<tbody>
<tr>
<td>More Unrestricted Commercial Lives Than Symbicort</td>
<td>More Unrestricted Medicare Part D Lives Than Symbicort</td>
</tr>
</tbody>
</table>

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

Important Safety Information (cont’d)

ADVERSE REACTIONS (cont’d)
- Additional adverse reactions (≥2% incidence) reported in subjects taking BREO 200/25 in a 24-week trial included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia; and with BREO 100/25 or 200/25 in a 12-month trial included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.
- In a 24- to 76-week trial of subjects with ≥1 asthma exacerbations in the past year, asthma-related hospitalizations occurred in 1% of subjects taking BREO 100/25. No asthma-related deaths or intubations were observed.

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

USE IN SPECIFIC POPULATIONS
- BREO is not indicated for children and adolescents; the safety and efficacy in patients aged ≤17 years have not been established.
- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.


PAY NO MORE THAN $10 A MONTH

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

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

Discover how at www.24hourworld.com

BREO ELLIPTA was developed in collaboration with INNOVIVA

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BRED ELIPTA
(fluticasone furoate and vilanterol inhalation powder)

The following is a brief summary only and is focused on the asthma indication; see full prescribing information for complete product information.

INDICATIONS AND USAGE

1.2 Treatment of Asthma: BRED is indicated for the once-daily treatment of asthma in patients aged 12 years and older with whom there are inadequate responses to previously used corticosteroids such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta₂-adrenergic agonist (LABA). Important Limitation of Use: BRED is NOT indicated for the relief of acute symptoms of asthma.

4 CONTRAINDICATIONS

The use of BRED is contraindicated in the following conditions: primary treatment of status asthmaticus or other acute episodes of chronic obstructive pulmonary disease (COPD) or asthma where intubation is required (see Warnings and Precautions (5.2)) and severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients (see Warnings and Precautions (5.5)).

5.15 Osteoporosis:

The risk of osteoporosis is associated with ICS therapy, particularly in women who are post-menopausal. The safety of these patients is not known. Special attention should be paid to patients with low bone density prior to initiating BRED, and these patients should be monitored for future BRED use. The risk of osteoporosis is also increased in post-menopausal women and the elderly. Continued monitoring for post-menopausal patients taking BRED is recommended. Special attention should be paid to patients with low bone density prior to initiating BRED, and these patients should be monitored for future BRED use. The risk of osteoporosis is also increased in post-menopausal women and the elderly. Continued monitoring for post-menopausal patients taking BRED is recommended.

5.16 Acne:

Acne may be more common in patients using BRED for the treatment of asthma. Acne was reported as a common adverse reaction in clinical trials when BRED was used as monotherapy for the treatment of asthma (13%).

5.17 Effect on Growth: Ora! inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. (See Use in Specific Populations (8.4) of full prescribing information.)
6.2 Clinical Trials Experience in Asthma: (cont'd) Of the 1,019 subjects, 60% were female and 88% were white. The mean age was 46 years. In Trial 2, adverse reactions (≥2%) in incidence in subjects with asthma taking BREO 200/25 (n = 346), BREO 100/25 (n = 344), or fluticasone furoate 100 mcg (n = 347), respectively, were: headache: 8%, 8%, 9%; nausea: 7%, 6%, 5%; back pain: 3%, 1%, 2%; myalgia: 1%, 1%, 2%; dyspepsia: 2%, 2%, 1%; cough: 1%, 2%, 1%. 24-Week Trial: This was a 24-week trial that evaluated the efficacy of BREO 200/25 once daily, fluticasone furoate 250 mcg once daily, and fluticasone propionate 500 mcg twice daily in adult and adolescent subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years. Adolescents (aged 12 to 17 years) made up 16% of the population. Additions 1 to 24-76 week trials, subjects received BREO 200/25 (n = 1,800) or fluticasone furoate 100 mcg (n = 1,800) (Trial 5). Subjects participating in this trial had a history of 1 or more asthma exacerbations that required treatment with oral systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to entry. Overall, 67% were female and 73% were white; the mean age was 42 years; adolescents (aged 12 to 17 years) made up 14% of the population. Of the adolescents aged 12 to 17 years, 12% were male and 88% were white; these were included in Trial 5, breo not approved for use in this age group (see in Specific Populations (8.4). Asthma-related hospitalizations occurred in 2% of the subjects treated with BREO 200/25 or BREO 250/25 for 12 months included pyrexia, back pain, extrapyramidal effects, upper abdominal pain, respiratory tract infection, anaphylaxis, pyrexia, and arthralgia. 12-Month Trial: Long-term safety data are based on a 12-month trial that evaluated the safety of BREO 100/25 once daily, fluticasone furoate 250 mcg once daily, and fluticasone propionate 500 mcg twice daily in adult and adolescent subjects with asthma (Trial 4). Overall, 63% were female and 67% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions noted for Trial 4, headache, 8%, 8%, 9%; nausea: 7%, 6%, 5%; back pain: 3%, 1%, 2%; myalgia: 1%, 1%, 2%; dyspepsia: 2%, 2%, 1%; and cough: 1%, 2%, 1% occurred in ≥2% of the subjects treated with BREO 200/25 or BREO 250/25 for 24 months included pyrexia, back pain, extrapyramidal effects, upper abdominal pain, respiratory tract infection, anaphylaxis, pyrexia, and arthralgia. 12-Month Trial: Long-term safety data are based on a 12-month trial that evaluated the safety of BREO 100/25 once daily, fluticasone furoate 250 mcg once daily, and fluticasone propionate 500 mcg twice daily in adult and adolescent subjects with asthma (Trial 4). Overall, 63% were female and 67% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions noted for Trial 4, headache, 8%, 8%, 9%; nausea: 7%, 6%, 5%; back pain: 3%, 1%, 2%; myalgia: 1%, 1%, 2%; dyspepsia: 2%, 2%, 1%; and cough: 1%, 2%, 1%.
burden with a resultant decrease in quality-of-life. Extrapulmonary co-morbidities, such as obesity, nicotine use, GERD, allergic rhinitis, chronic rhinosinusitis, sleep apnea, anxiety/depression, females of older age, vocal cord dysfunction (VCD), and type 2 diabetes mellitus (T2DM) have been shown to increase exacerbation frequency, missed days of school/work, and lessened quality-of life. Of these co-morbidities, that latter has garnered recent attention as a focal point for asthma management.

As many as one in six asthmatics has T2DM, and the obvious impact of oral/systemic corticosteroids runs counter to the treatment armamentarium for difficult-to-control asthma. Furthermore, patients with concomitant T2DM and asthma have poor glycemic control, higher risk of pneumococcal pneumonia, and poor quality-adjusted life expectancy (Black MH et al. Pediatrics. 2014;128:e839-47) Of growing interest is the use of metformin in the treatment of Type 2 diabetes mellitus in patients with asthma. Metformin attenuates eosinophilic airway inflammation and theoretically inhibits airway remodeling through AMP-activated protein kinase (Li, et al. Respirology. 2016;21:1210).

The management of this heterogeneous group of patients with difficult-to-control asthma and the aforementioned comorbidities underscores the need for interdisciplinary collaboration as well as orchestration with specialty providers (family/internal medicine, GI, ENT, endocrine, psych/mental health, et al). Further studies are needed to evaluate the anti-inflammatory properties of metformin and its role in asthma management and improvement in outcome.

David W. Unkle, MSN, APRN, FCCP
Steering Committee Chair

New section editor for Pulmonary Perspectives®

We are pleased to announce Corey Kershaw, MD, as the new Section Editor for Pulmonary Perspectives. Dr. Kershaw is the Medical Director of the Medical Intensive Care Unit at Clements University Hospital and an Associate Professor, Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, in Dallas, Texas. He currently serves on the American College of Chest Physicians Interstitial and Diffuse Lung Disease Network. Dr. Kershaw’s research interests revolve around clinical trials for the treatment of idiopathic pulmonary fibrosis and other fibrosing interstitial lung diseases.

We thank Nitin Puri, MD, FCCP, for his outstanding service as the Pulmonary Perspectives Section Editor for the previous 3 years.
CPT® and ICD-10 coding for endobronchial valves

The FDA recently approved endobronchial valves for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little to no collateral ventilation. There are CPT® and ICD 10 codes that are appropriate to report these new services. CPT® codes typically are not product or device specific and the codes below apply to current and future FDA approved endobronchial valves with similar clinical indications and intent for the treatment of emphysema.

To be a candidate for the currently approved service, patients must have little to no collateral ventilation between the target and adjacent lobes. In some patients, this can be determined by a quantitative CT analysis service to assess emphysematous destruction and fissure completeness. If there is radiographic evidence of a complete fissure and anatomic isolation of the treatment target, a bronchoscopy assessment will be made on the patient. A bronchial blocking balloon and flow detection system is used to confirm that the patient has little to no collateral ventilation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31634</td>
<td>Bronchoscopy, rigid with balloon occlusion, with assessment of air leak or flexible, including fluoroscopic guidance, when performed, with administration of occlusive substance (eg, fibrin glue), if performed (Do not report 31634 in conjunction with 31647, 31651 at the same session)</td>
</tr>
</tbody>
</table>

If the bronchial blocking technique shows evidence of collateral ventilation, the patient would be discharged without valve placement. In that scenario the appropriate CPT® code would be 31634.

If the patient is determined not to have collateral ventilation, the valve procedure would proceed, followed by a minimum three-day inpatient stay to monitor for possible side effects. The appropriate CPT codes for placing, and removing FDA approved valves are:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31647</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe</td>
</tr>
<tr>
<td>+31651</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe (Use 31651 in conjunction with 31647)</td>
</tr>
<tr>
<td>31648</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe</td>
</tr>
<tr>
<td>+31649</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure) (Use 31649 in conjunction with 31648)</td>
</tr>
</tbody>
</table>

The table below identifies potential ICD-10-CM diagnosis codes for emphysema. Applicability and usage of these codes may vary per case. Hospitals and physicians also should check and verify current policies and requirements with the payer for any patient who will be treated with endobronchial valves.

**Emphysema ICD-10-CM Diagnosis Codes**

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J43.0</td>
<td>Unilateral pulmonary emphysema</td>
</tr>
<tr>
<td>J43.1</td>
<td>Panlobular emphysema</td>
</tr>
<tr>
<td>J43.2</td>
<td>Centrilobular emphysema</td>
</tr>
<tr>
<td>J43.8</td>
<td>Other emphysema</td>
</tr>
<tr>
<td>J43.9</td>
<td>Emphysema, unspecified</td>
</tr>
</tbody>
</table>

The CHEST/ATS Clinical Practice Committee provided information for this article.
Crack pneumonia cases faster.

Get fast, comprehensive results with the BioFire® FilmArray® Pneumonia Panel.

When patients present with severe respiratory symptoms, an accurate diagnosis can set the stage for clinical success. The BioFire Pneumonia Panel utilizes a syndromic approach—simultaneously testing for different infectious agents that can cause similar symptoms. The BioFire Pneumonia Panel tests for bacterial and viral infections, as well as antimicrobial resistance genes, directly from lower-respiratory specimens. You get the helpful answers you need all in about one hour—ultimately aiding in diagnosis and subsequent treatment.

Learn more at biofiredx.com

The BioFire Pneumonia Panel

<table>
<thead>
<tr>
<th>Bacteria (semi-quantitative)</th>
<th>Atypical Bacteria (qualitative)</th>
<th>Viruses (qualitative)</th>
<th>Resistance Markers</th>
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<tbody>
<tr>
<td>Acinetobacter calcoaceticus</td>
<td>Chlamydia pneumoniae</td>
<td>Adenovirus</td>
<td>Carbapenemase</td>
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<td>baumannii complex</td>
<td>Legionella pneumophila</td>
<td>Coronavirus</td>
<td>IMP</td>
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<td>Enterobacter cloacae</td>
<td>Mycoplasma pneumoniae</td>
<td>Human Metapneumovirus</td>
<td>KPC</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
<td>Human Rhinovirus/Enterovirus</td>
<td>NDM</td>
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<tr>
<td>Haemophilus influenzae</td>
<td></td>
<td>Influenza A</td>
<td>Oxa48-like</td>
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<td>Klebsiella aerogenes</td>
<td></td>
<td>Influenza B</td>
<td>VIM</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td></td>
<td>Parainfluenza virus</td>
<td>ESBLS</td>
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<tr>
<td>Klebsiella pneumoniae group</td>
<td></td>
<td>Respiratory Syncytial virus</td>
<td>CTX-M</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
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<td></td>
<td>MRSA</td>
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<tr>
<td>Proteus spp.</td>
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<td></td>
<td>mecA/C and MREJ</td>
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<td>Pseudomonas aeruginosa</td>
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<td>Serratia marcescens</td>
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<td>Staphylococcus aureus</td>
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<td>Streptococcus agalactiae</td>
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<tr>
<td>Streptococcus pyogenes</td>
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