Quality of care not tied to pneumonia readmissions

Readmission causes are multifaceted.

BY SHANNON AYMES
Frontline Medical News

Lower quality of care was not associated with pneumonia readmissions, according to a study using a commercially available software program to examine possibly preventable readmissions.

Rates of hospital readmission are now being used to demonstrate hospital performance and the Centers for Medicare & Medicaid Services may even penalize hospitals with high rates of readmissions. As a result, it has become increasingly important to recognize clinical situations that may lead to a potentially preventable readmission.

The Potentially Preventable Readmission (PPRs) software was developed by 3M Health Information Systems to identify such cases and is being adopted by some state Medicaid programs. Dr. Ann M. Borzechski of the Center for Healthcare Organization and Implementation Research in Bedford, Mass., and her colleagues sought to understand if patients with pneumonia flagged by the PPR software as preventable readmissions were associated with failures in the process of care.

See Readmissions • page 9

Bevacizumab prolongs survival in unresectable mesothelioma

BY SUSAN LONDON
Frontline Medical News

DENVER – Adding the antiangiogenic antibody bevacizumab to chemotherapy improves outcomes in patients who have unresectable mesothelioma, with little downside, according to results of MAPS (the Mesothelioma Avastin Plus Pemetrexed-Cisplatin Study).

Median overall survival in the multicenter randomized phase III trial was 2.75 months longer for patients given bevacizumab in addition to the doublet of pemetrexed plus cisplatin, first author Dr. Arnaud Scherpereel reported at a world conference on lung cancer.

This benefit was achieved with only a small increase in the rate of grade 3 or 4 toxicity and no detrimental to quality of life.

“We feel that the treatment” See Mesothelioma • page 11
HELP HER WRITE FUTURE CHAPTERS

OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids¹

OPSUMIT® (macitentan) is the only ERA approved to delay disease progression as both monotherapy and in combination with PDE-5 inhibitors or inhaled prostanoids. It is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.

- Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
- Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5: phosphodiesterase type 5; SC: subcutaneous; SERAPHIN: Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; ULN: upper limit of normal; WHO: World Health Organization.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
SERAPHIN: The first long-term outcome trial in PAH (average treatment 2 years) to demonstrate the use of both monotherapy and combination therapy to delay disease progression.\(^1\)\(^2\)

Patients were treated with OPSUMIT monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids.\(^3\)

- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients.\(^1\)
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years.\(^1\)
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study.\(^1\)

SERAPHIN was a randomized, double-blind, placebo-controlled, event-driven outcome study to assess the effect of OPSUMIT on disease progression (time to first significant morbidity or mortality event), as defined by death, atrial septostomy, lung transplantation, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).\(^1\)\(^2\)

WARNINGS AND PRECAUTIONS (continued)

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN was 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × ULN was 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
WARNINGS AND PRECAUTIONS (continued)

Hemoglobin Decrease
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
**INDICATION** (continued)

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

**ADVERSE REACTIONS**

- Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

**DRUG INTERACTIONS**

- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.

- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

**References:**

CI: confidence interval; CYP: cytochrome P450; FC: functional class; HIV: human immunodeficiency virus.

**Please see important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.**

OPSUMIT is a registered trademark of Actelion Pharmaceuticals, Ltd.
© 2015 Actelion Pharmaceuticals US, Inc. All rights reserved. MAC-00701 0515

---

**OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids**

**Subgroup analysis of the primary endpoint in the SERAPHIN study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>OPSUMIT No. of events/No. of patients</th>
<th>Placebo No. of events/No. of patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment effect</td>
<td></td>
<td>76/242</td>
<td>116/250</td>
<td>0.55 (0.41, 0.73)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant PAH therapy at baseline</td>
<td></td>
<td>50/154</td>
<td>68/154</td>
<td>0.62 (0.43, 0.89)</td>
</tr>
<tr>
<td>Combination with PDE-5 inhibitors and/or inhaled or oral prostanoids†</td>
<td></td>
<td>26/88</td>
<td>48/96</td>
<td>0.45 (0.28, 0.72)</td>
</tr>
</tbody>
</table>

†The OPSUMIT indication includes combination with phosphodiesterase-5 inhibitors or inhaled prostanoids, but not oral prostanoids.

In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)... **Don’t delay, treat today—keep disease progression in mind from the start of therapy in FC II and III patients.**

OPSUMIT is approved for use as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids†
The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

BRIEF SUMMARY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see Contraindications (Pregnancy), Warnings and Precautions (Embryofetal Toxicity), Use in Specific Populations (Pregnancy)].
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception [see Use in Special Populations (Females and Males of Reproductive Potential)].
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) [see Warnings and Precautions (OPSUMIT REMS Program)].

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class III-IV symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (8%), and PAH caused by congenital heart disease with repaired shunts (8%).

CONTRAINDICATIONS

- Pregnancy
  - OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus [see Warnings and Precautions (Embryo-fetal Toxicity) and Use in Specific Populations (Pregnancy)].

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy. Ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see Dosage and Administration section 2.2 in full Prescribing Information and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

OPSUMIT REMS Program

For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity [see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)].

Notable requirements of the OPSUMIT REMS Program include the following:
- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (Females and Males of Reproductive Potential)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated. Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT in PAH, OPSUMIT 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated [see Adverse Reactions (Clinical Trial Experience)].

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts

Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility [see Use in Specific Populations (Females and Males of Reproductive Potential) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:
- Embryo-fetal Toxicity [see Warnings and Precautions (Embryo-fetal Toxicity)]
- Hepatotoxicity [see Warnings and Precautions (Hepatotoxicity)]
- Decrease in Hemoglobin [see Warnings and Precautions (Hemoglobin Decrease)]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 common clinical practice.

Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.5 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT than on placebo by ≥3%.

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

<table>
<thead>
<tr>
<th>Aminotransferases</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 × ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;8 × ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Table 2: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OPSUMIT. 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.

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash)
Respiratory, thoracic and mediastinal disorders: nasal congestion...
**DRUG INTERACTIONS**

**Strong CYP3A4 Inducers**

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetics)].

**Strong CYP3A4 Inhibitors**

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV viruses like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see Clinical Pharmacology (Pharmacokinetics)]. Use other P450 treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications (Pregnancy)].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

**Nursing Mothers**

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites were present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan to nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

**Pediatric use**

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Females and Males of Reproductive Potential**

**Females**

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intravaginal devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications (Pregnancy)].

Animal Data

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

**Testicular effects:** Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Counts) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

**OVERDOSAGE**

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (80 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**Special Populations**

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

**Renal impairment:** Exposure to macitentan and its active metabolite in patients with severe renal impairment (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

**OPSUMIT**

Hepatic impairment: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

**Drug Interactions**

**In vitro studies**

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1). Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

**In vivo studies**

Effect of other drugs on macitentan: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

**Figure 1**

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Macitentan</th>
<th>Active Metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>AUC</td>
<td>AUC</td>
<td>No-dose adjustment</td>
</tr>
<tr>
<td>Cyclosporine-A</td>
<td>AUC</td>
<td>AUC</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>AUC</td>
<td>AUC</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rifampin</td>
<td>AUC</td>
<td>AUC</td>
<td>Avoid</td>
</tr>
</tbody>
</table>

Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

Effect of macitentan on other drugs

Warfarin: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

**Mutagenesis:** Macitentan was not genotoxic in a standard battery of in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vivo micronucleus test in rats.

**Impairment of Fertility:** Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected. Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

**Animal Toxicology**

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

**Manufactured for:**

Actelion Pharmaceuticals US, Inc.

5000 Shoreline Court, Ste. 200

South San Francisco, CA 94080, USA

ACT20150219


*OPSUMIT is a registered trademark of Actelion Pharmaceuticals Ltd. © 2015 Actelion Pharmaceuticals US, Inc. All rights reserved. MAC-00646325
Physician Quality Reporting System (PQRS)
CMS proposes to audit not only physician participants, but also vendors who submit quality measure data on behalf of doctors, under the 2016 proposed fee schedule. The agency recommends that vendors make available contact information for each eligible practitioner on behalf of whom it submits data and retain data submitted to CMS for PQRS for 7 years.

Doctors who fail to report on nine quality measures for PQRS will not automatically face trouble, according to Daniel F. Shay, a health law attorney in Philadelphia. In general, individual physicians in PQRS must report on at least nine measures covering three National Quality Strategy (NQS) domains for at least 50% of their Medicare patient base. But if fewer than nine measures are reported, physicians have the chance to explain themselves.

“In some cases, a practice may not have at least nine measures that apply to it,” Mr. Shay said. “The [eligible practitioner] would then be able to report on fewer than nine measures, but would be subject to the measure application validity process, which basically means CMS audits the provider to prove they couldn’t have reported on all of the required measures.”

Also, CMS proposes extending participation in PQRS to doctors who practice in critical access hospitals, according to the 2016 proposed fee schedule. PQRS is a voluntary quality reporting program that applies adjustments to payments based on benchmarks. CMS is suggesting that physicians who practice in certain critical access hospitals now have the option to participate in the program—such doctors were previously excluded.

Incident to service
When overseeing care that is “incident to” service, CMS proposes that billing physicians also act as supervising physicians. The proposal could impact group practices who do not typically use that structure, said Washington health law attorney Julie E. Kass during the AHLA webinar.

Incident to is defined as services furnished incident to a physician’s professional services over the course of a patient’s diagnosis or treatment. Medicare pays for services rendered by employees of a physician only when all incident to criteria are met. Those criteria include that services rendered by nonphysicians are under the direct supervision of a physician physically in the same office suite. In the proposed 2016 rule, CMS seeks to clarify that the billing physician must be the same physician who supervises the ancillary personnel. Previously, group practices may have billed under the provider who ordered the treatment, according to Ms. Kass.

“It sounds simple, but then you put it into the context of what happens in a real life practice,” she said. “I think a lot of practices, in operation- alizing this rule, have generally used the ordering physician as the physician who billed for the service without paying a lot of attention to who was the actual supervising physician.”

Group practices may want to rethink how they bill for incident to services, and ensure the billing physician is the one who supervises the treatment, she advised.

The Stark Law
Proposed changes to regulations implementing the Stark Law could make it easier for physicians to hire nonphysician providers (NPP) to provide primary care. Under the fee schedule proposal, hospitals would be allowed to assist in the recruitment of health professionals for physician practices. Currently, hospitals may not because remuneration could be considered a compensation relationship between the hospital and physician practice. The proposed change aims to promote care team collaboration and help curb primary care shortages. The exception would permit recruitment assistance and retention payment from a hospital, rural health clinic, or federally qualified health center to a physician practice to employ an NPP. However, the NPP would have to be a bona fide employee of the physician practice and provide primary care services. CMS defines an NPP as a physician assistant, nurse practitioner, clinical nurse specialist, or certified nurse-midwife.

CMS is also recommending a cap on the total remuneration and duration of assistance provided.

Value-Based Payment Modifier Program
CMS proposes a new way to determine the extent of payment cuts and bonuses in the Value-Based Payment Modifier Program. The program evaluates the performance of solo practitioners and groups on the quality and cost of care they provide to fee-for-service Medicare patients.

In 2016, the agency proposes to adjust payments based on the size of the participating group and to determine that size by reviewing claims data and its Provider Enrollment, Chain, and Ownership System (PECSO)—generated list. CMS would apply whichever number is lower in PECOS or claims data.
No link to inferior quality of care

The researchers conducted a cross-sectional retrospective observational study with Veterans Affairs electronic medical record (EMR) data from October 2005 to September 2010. Patients with diagnoses of pneumonia and a 30-day readmission were identified and then flagged as PPR-yes (for example, readmissions associated with quality of care problems) vs. PPR-no, using the 3M PPR software. A tool to measure quality of care was applied to 100 random readmissions abstracted for full review. The study was published online in BMJ Quality and Safety.

Of all the pneumonia readmission cases, 72% were PPR-yes vs. 77% of the 100 abstracted cases. There were no significant differences between the groups other than a trend toward more comorbidity in the PPR-yes group.

After researchers adjusted for comorbidities and demographics, they noted no significant difference in quality of care between the PPR-yes and PPR-no groups. Interestingly, the PPR-yes group had slightly higher quality scores than did the PPR-no group (total scores, 71.2 vs. 65.8 respectively, \( P = .14 \)).

The authors write, ‘Among veterans readmitted after a pneumonia discharge, we found no significant difference in quality of care, as measured by processes of care received during the index admission and after discharge, between cases flagged as PPRs and nonflagged cases. ‘Indeed, contrary to our hypothesis, quality scores were slightly higher among PPR-flagged cases.’

The authors emphasized that causes of readmissions are multifaceted and many aspects may be out of the control of the hospital. However, they noted a concern for a lack of postdischarge documentation and emphasized the need for thorough documentation at all levels of care.

The authors report no competing interest. The study was funded by the U.S. Department of Veterans Affairs Health Service Research and Development Service.
HIT risk strongly correlated with body mass index

BY SHARON WORCESTER
Frontline Medical News

AT THE AAST ANNUAL MEETING

LAS VEGAS – High body mass index is strongly associated with increased rates of heparin-induced thrombocytopenia, based on findings from a review of prospectively collected data from surgical and cardiac intensive care unit patients presumed to have the condition.

Of 304 patients included in the review, 36 (12%) were positive for heparin-induced thrombocytopenia (HIT). The rates increased in tandem with BMI. For example, the rate was 0% among 9 underweight individuals (BMI less than 18.5 kg/m²), 8% among 119 normal-weight individuals (BMI of 18.5-24.9 kg/m²), 11% among 98 overweight individuals (BMI of 25-29.9 kg/m²), 18% among 67 obese individuals (BMI of 30-39.9 kg/m²), and 36% among 11 morbidly obese individuals (BMI of 40 kg/m² or greater), Dr. Matthew B. Bloom reported at the annual meeting of the American Association for the Surgery of Trauma.

The odds of HIT were 170% greater among obese patients, compared with normal-weight patients (odds ratio, 2.67), and 660% greater among morbidly obese patients, compared with normal-weight patients (odds ratio, 6.98), said Dr. Bloom of Cedars-Sinai Medical Center, Los Angeles.

Logistic regression showed that each 1-unit increase in BMI was associated with a 7.7% increase in the odds of developing HIT, he noted.

Additionally, an anti-heparin/PF4 (platelet factor 4) antibody OD (optical density) value of 2.0 or greater, but not of 0.4 or greater or 0.8 or greater, was also significantly increased with BMI, and in-hospital mortality increased significantly with BMI above normal, he said.

Warkentin 4T scores used to differentiate HIT from other types of thrombocytopenia were not found to correlate with changes in BMI in this study, nor were deep vein thrombosis, pulmonary embolism, or stroke.

The increase in PF4 with increasing BMI may be a marker for overall increasing levels of circulating antibodies in the obese ICU population, but more biochemical studies are needed to tease this out, he said.

Patients included in the review were all those admitted to the surgical and cardiac ICUs at Cedars-Sinai over a more than 7-year period. They had a mean age of 62.1 years, 59% were men, and their mean BMI was 27 kg/m².

The findings are among the first to show a strong association between BMI and HIT in ICU patients, Dr. Bloom said, noting that several other studies have shown that obesity is linked with increased incidence and increased severity of immune-mediated diseases, including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.

“BMI may be an important new clinical variable for estimating the pre-test probability of HIT, and perhaps in the future, patient ‘ thickness’ could be considered a new ‘T’ in the 4T score,” he concluded.

Dr. Bloom reported having no disclosures.

sworcester@frontlinemedcom.com

Clothing may transmit respiratory syncytial virus in NICU

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Clothing worn by caregivers and visitors may be an important vehicle for the transmission of respiratory syncytial virus in the neonatal intensive care unit, according to findings from a prospective study conducted in an Australian hospital.

In an effort to identify potential sources of RSV transmission and to facilitate development of infection control strategies, the investigators swabbed all health personnel, every third neonate and their caregivers/visitors while they are in the NICU, noting that caregivers and visitors are not required to change clothing when they walk into the NICU.

Of 304 patients included in the review, 36 (12%) were positive for heparin-induced thrombocytopenia (HIT). The rates increased in tandem with BMI. For example, the rate was 0% among 9 underweight individuals (BMI less than 18.5 kg/m²), 8% among 119 normal-weight individuals (BMI of 18.5-24.9 kg/m²), 11% among 98 overweight individuals (BMI of 25-29.9 kg/m²), 18% among 67 obese individuals (BMI of 30-39.9 kg/m²), and 36% among 11 morbidly obese individuals (BMI of 40 kg/m² or greater), Dr. Matthew B. Bloom reported at the annual meeting of the American Association for the Surgery of Trauma.

The odds of HIT were 170% greater among obese patients, compared with normal-weight patients (odds ratio, 2.67), and 660% greater among morbidly obese patients, compared with normal-weight patient...
10 years ago, Boehringer Ingelheim made history in COPD treatment, but that was only the beginning...
Contains tiotropium, the active ingredient in

**INDICATION**
Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray is a combination of tiotropium, an anticholinergic, and olodaterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

**Important Limitations of Use**
STIOLTO is NOT indicated to treat acute deterioration of COPD and is not indicated to treat asthma.

**IMPORTANT SAFETY INFORMATION**

**WARNING: ASTHMA-RELATED DEATH**
Long-acting beta2-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma.

**CONTRAINDICATION**
All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. STIOLTO is contraindicated in patients with hypersensitivity to tiotropium, ipratropium (atropine derivatives), olodaterol, or any component of this product.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO.

**WARNINGS AND PRECAUTIONS**
STIOLTO should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition, or used as rescue therapy for acute symptoms. Acute symptoms should be treated with an inhaled short-acting beta2-agonist. Patients who have been taking inhaled, short-acting beta2-agonists on a regular basis should discontinue the regular use of these drugs and use them only for acute respiratory symptoms.

STIOLTO should not be used more often or at higher doses than recommended, or in conjunction with other LABA as an overdose may result.

Immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO. If such a reaction occurs, discontinue therapy with STIOLTO and consider alternative treatments. Patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO.

If paradoxical bronchospasm occurs, STIOLTO should be discontinued immediately.

STIOLTO can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STIOLTO may need to be discontinued.

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.
“There was no significant difference between the two arms in the percentage of drug delivery or the percentage of patients having second-line treatment which could explain the increase of survival in the bevacizumab arm,” he reported.

The proportion of patients experiencing grade 3 or 4 toxicity was higher in the bevacizumab arm, according to Dr. Scherpereel. Furthermore, in terms of quality of life measures, patients in the bevacizumab arm had a greater improvement in fatigue from baseline ($P = .046$) and scores for other measures did not differ between arms.

“We did not find some predictive clinical or biological marker of bevacizumab benefit for this study,” he said. In particular, patients’ pretreatment levels of vascular endothelial growth factor (VEGF) did not identify a group more likely to benefit. But an ongoing companion study is still evaluating other biomarkers, such as mesothelin and endocan, he added.

Dr. Scherpereel disclosed that he and coinvestigators had affiliations with Roche and other companies. Roche supplied bevacizumab and a research grant for the biomarker studies.
Prolonged sepsis increased inpatient mortality risk

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – The longer patients have sepsis, the more likely they are to die while in the hospital, a retrospective, single-center study showed. However, lower respiratory tract infection, methicillin-resistant Staphylococcus aureus infection, Charlson score, and time to treatment with antibiotics were not significantly associated with increased odds for mortality.

“Sepsis is a life-threatening acute condition that is commonly associated with inpatient mortality,” said Joseph J. Carreno, Pharm.D., said in an interview in advance of the annual Interscience Conference on Antimicrobial Agents and Chemotherapy. “To date, numerous interventions have evaluated the impact of interventions on sepsis-related mortality. However, few have...”
other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in ≥3% of patients in clinical studies are listed below.

- Bronchospasm, laryngitis, sinusitis; mediastinal disorders: epistaxis, pharyngitis, dysphonia, dysphagia, gastroesophageal reflux disease, gingivitis, tissue disorders and connective tissue disorders: dehydration; nervous system disorders: dizziness, insomnia, eye disorders: glaucoma, intraocular pressure increased, vision blurred.

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in <3% of patients in clinical studies are listed below: Bronchospasm, laryngitis, sinusitis; dermatological disorders: rash, urticaria; eye disorders: conjunctivitis and/or corneal disorders; ear and mastoid disorders: hearing impairment; gastrointestinal disorders: diarrhea, abdominal pain.

Table 1: Number and frequency of adverse drug reactions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>STIOLTO RESPIMAT (once daily)</th>
<th>Tiotropium (5 mcg once daily)</th>
<th>Olodaterol (5 mcg once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Body system (adverse drug reactions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>128 (12.0)</td>
<td>121 (11.7)</td>
<td>137 (13.2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>40 (3.9)</td>
<td>45 (4.4)</td>
<td>31 (3.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>37 (3.6)</td>
<td>19 (1.8)</td>
<td>35 (3.4)</td>
</tr>
</tbody>
</table>

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in ≥3% of patients in clinical studies are listed below.

- Bronchospasm, laryngitis, sinusitis; dermatological disorders: rash, urticaria; eye disorders: conjunctivitis and/or corneal disorders; ear and mastoid disorders: hearing impairment; gastrointestinal disorders: diarrhea, abdominal pain.

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in <3% of patients in clinical studies are listed below: Bronchospasm, laryngitis, sinusitis; dermatological disorders: rash, urticaria; eye disorders: conjunctivitis and/or corneal disorders; ear and mastoid disorders: hearing impairment; gastrointestinal disorders: diarrhea, abdominal pain.

Table 1: Number and frequency of adverse drug reactions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>STIOLTO RESPIMAT (once daily)</th>
<th>Tiotropium (5 mcg once daily)</th>
<th>Olodaterol (5 mcg once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Body system (adverse drug reactions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>128 (12.0)</td>
<td>121 (11.7)</td>
<td>137 (13.2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>40 (3.9)</td>
<td>45 (4.4)</td>
<td>31 (3.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>37 (3.6)</td>
<td>19 (1.8)</td>
<td>35 (3.4)</td>
</tr>
</tbody>
</table>

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in ≥3% of patients in clinical studies are listed below.

- Bronchospasm, laryngitis, sinusitis; dermatological disorders: rash, urticaria; eye disorders: conjunctivitis and/or corneal disorders; ear and mastoid disorders: hearing impairment; gastrointestinal disorders: diarrhea, abdominal pain.

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in <3% of patients in clinical studies are listed below: Bronchospasm, laryngitis, sinusitis; dermatological disorders: rash, urticaria; eye disorders: conjunctivitis and/or corneal disorders; ear and mastoid disorders: hearing impairment; gastrointestinal disorders: diarrhea, abdominal pain.

Table 1: Number and frequency of adverse drug reactions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>STIOLTO RESPIMAT (once daily)</th>
<th>Tiotropium (5 mcg once daily)</th>
<th>Olodaterol (5 mcg once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Body system (adverse drug reactions)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>128 (12.0)</td>
<td>121 (11.7)</td>
<td>137 (13.2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>40 (3.9)</td>
<td>45 (4.4)</td>
<td>31 (3.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>37 (3.6)</td>
<td>19 (1.8)</td>
<td>35 (3.4)</td>
</tr>
</tbody>
</table>
TCAD regimen shows promise against H3N2 flu

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Triple-combination antiviral drug therapy offers a broad-spectrum treatment option for H3N2 variant influenza virus, according to findings from an in vitro study.

The findings suggest that the combination could play an important role in the event of an influenza pandemic, Carrie Sitz reported in a poster at the International Conference on Emerging Infectious Diseases.

After a human infection with the novel A/H3N2 variant was reported in 2011, and trivalent inactivated influenza vaccine was found to be of limited use, as it provided protection against H3N2 but not the H3N2 variant (H3N2v) as it provided protection against H3N2, the TCAD regimen was considered.

A custom control experiment in the absence of the drugs was also performed.

Of note, amantadine had no activity as a single agent against H3N2v, even at 100 mcg/mL, the highest dose tested. However, amantadine did contribute to the synergy of the TCAD regimen. This effect was concentration dependent; the potential synergy volume increased steadily and significantly from about 300 to about 450, to about 575, and to about 600 as the amantadine concentration increased from +0.32, to +1.0, to +3.2, to +10, Ms. Sitz noted, adding that this may indicate that amantadine, which is known to have widespread resistance, can still play a therapeutic role in the setting of the TCAD regimen.

Vaccines are usually an effective safeguard against seasonal influenza but may be inadequate in seasons when a novel influenza emerges, resulting in compromised standard of care for treating the emergent virus, she said, noting that this is especially true in immunocompromised patients.

These issues point to the likelihood that we may be unprepared for a novel influenza virus displaying both virulence and transmissibility, she added.

The current findings suggest that TCAD, which has previously been shown to be effective against seasonal and H5 influenza strains, is a broad-spectrum treatment option that could potentially play a role in pandemic preparedness. The mechanism by which oseltamivir carbonylate and ribavirin potentiate amantadine in combination therapy is unknown, and further testing is needed for evaluation, she concluded.

This study was sponsored by the Armed Forces Health Surveillance Center. The authors had no disclosures.

sworcester@frontlinemedcom.com

60% risk reduction

Pertussis from page 1

Up-to-date status was protective against severe disease, defined as disease involving seizures, encephalopathy, pneumonia, or hospitalization, in children aged 7 months to 6 years, who had about a 60% reduction in risk, compared with those who were not up to date. Up-to-date status also reduced the risk of posttussive vomiting, which sometimes accompanies severe coughing fits, by about 25% in those aged 19 months to 64 years, she said, adding that the risk of vomiting after coughing was about 38% lower in this age group when patients received antibiotic treatment within 1 week of the start of the illness.

Dr. Eric Gartman, FCCP, comments: The conclusions from this study have significant implications in clinical medicine and may run contrary to the generally held belief that up-to-date vaccination status confers near-complete protection against the disease for which we are vaccinating. As such, it is apparent clinicians need to consider pertussis in all appropriate clinical presentations, and not be falsely reassured by vaccination history. While it certainly is encouraging that vaccination offers significant protection from severe disease and routinely should be recommended for our patients, it underscores that we all need to recognize the limitations of our efforts and the need for continued vaccine research and development.

The effect on posttussive vomiting was independent of antibiotic treatment timing, which further underscores the value of both rapid treatment and completion of the pertussis vaccination schedule, Dr. McNamara commented. Dr. McNamara reported having no disclosures.

sworcester@frontlinemedcom.com

DATA WATCH: Spending up for the most costly medical conditions

BY RICHARD FRANKI
Frontline Medical News

Spending for each of the five most costly medical conditions rose by at least 21% from 2002 to 2012, the Agency for Healthcare Research and Quality reported.

That smallest-of-the-five increase of 21% belonged to the most expensive of the five, heart conditions, which rose from $83.5 billion in 2002 (in 2012 dollars) to $101 billion in 2012. The largest-of-the-five increase went to cancer, which jumped 46% from $59.8 billion to $87.5 billion, with mental disorders showing the next-largest increase as costs rose 43% from $78.6 billion to $83.6 billion, according to data from the Medical Expenditure Panel Survey.

The same conditions made up the top five in both 2002 and 2012. The average expenditure per person affected actually went down slightly for mental disorders — from $1,887 to $1,849 — but the number of persons affected rose 45%, from 31.1 million in 2002 to 45.2 million in 2012, which was the largest increase among the five most costly conditions.

The number of people affected went down 1% for trauma-related disorders and 10% for asthma and chronic obstructive pulmonary disease and rose almost 18% for heart conditions and 42% for cancer, the AHRQ said.

rfranki@frontlinemedcom.com

Notes: Based on data from the Medical Expenditure Panel Survey. COPD = chronic obstructive pulmonary disease.
Source: Agency for Healthcare Research and Quality
What if your PAH patient may not have PAH?

A ventilation-perfusion (V/Q) scan can rule out chronic thromboembolic pulmonary hypertension (CTEPH) in patients diagnosed with PAH, which is the only form of pulmonary hypertension that can be potentially cured by surgery.¹

If you know what to look for, a V/Q scan makes it relatively easy to spot.¹

References:

As many as 1 out of every 25 of your previously treated PE patients (>3 months of anticoagulation²) may develop CTEPH.³,⁴

*Based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5). CTEPH did not develop after two years in any of the 132 remaining patients with more than 2 years of follow up.

VISIT scan4CTEPH.COM FOR MORE INFORMATION
Screening for CTEPH in Patients With Suspected Pulmonary Hypertension

presented by

RICHARD CHANNICK, MD

Richard N. Channick, MD, is Associate Professor of Medicine at Harvard Medical School, Boston, Massachusetts, and has been Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital in Boston since 2009.

CTEPH IS A FORM OF PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension is a form of pulmonary hypertension (PH), designated by the World Health Organization as Group 4 PH. There are 5 WHO Groups of PH: 1: Pulmonary arterial hypertension 2: PH due to left heart disease 3: PH due to lung diseases and/or hypoxia 4: CTEPH 5: PH with unclear multifactorial mechanisms

Recently, Klok et al have coined the term “post-pulmonary embolism syndrome” to describe chronic complications of pulmonary embolism (PE), involving permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function which are associated with symptoms of dyspnea and decreased exercise capacity. The most serious manifestation of this syndrome—and the most serious complication of acute PE—is chronic thromboembolic pulmonary hypertension, or CTEPH. As many as 1 in 25 survivors of acute PE may go on to develop CTEPH within 2 years.

Hemodynamically, CTEPH is most often defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. These levels must be obtained via right heart catheterization, and they must be observed in the presence of multiple chronic/organized, occlusive thrombi/emboli in the pulmonary arteries after at least 3 months of effective anticoagulation.

Symptoms of CTEPH are nonspecific and include dyspnea on exertion, fatigue, weakness, chest pain, syncope, hemoptysis, and lower-extremity edema. Among the risk factors for CTEPH are unprovoked or recurrent PE, young age at the time of first PE, and splenectomy.

CTEPH is unique among the five groups of PH insofar as it is the only form that is potentially curable—via pulmonary thromboendarterectomy (PTE, also known as pulmonary endarterectomy [PEA]), the treatment of choice for surgical candidates with CTEPH. It is this potential to effect a curative treatment that makes it imperative to suspect and screen for CTEPH—and to differentiate CTEPH from other forms of PH—when patients present with symptoms consistent with PH.

HOW DOES CTEPH DEVELOP?

CTEPH results after a single PE or recurrent PEs that create endothelialized residua that obstruct or substantially narrow pulmonary arteries. The absence or depletion of endogenous nitric oxide may contribute to endothelial dysfunction in CTEPH. Obstruction and narrowing of the pulmonary arteries drives pulmonary arterial pressures to abnormal levels and increases pulmonary vascular resistance (PVR). Over time, developing small vessel vasculopathy can lead to right ventricular afterload, progression of PH, and CTEPH. If CTEPH is unrecognized or left untreated, right ventricular dysfunction can progress, ultimately resulting in right heart failure.

HOW COMMON IS CTEPH?

Based on data from small observational studies that followed survivors of acute PE, incidence of CTEPH has been estimated to be 0.57% (N=866 survivors of acute PE observed) to 3.8% (N=314 survivors of acute PE observed)—or almost 1 in 25—within 2 years of the first acute event. A more recent, but smaller (N=146 acute PE survivors followed for 26 months) study found that 8 survivors of acute PE were suspected to have CTEPH, and 7 of these—or 4.8% of the study population—were confirmed to have CTEPH. Yet another study of survivors of acute PE (N=104) saw 5.8% of patients develop CTEPH within 2 years. Further follow-up saw an additional 4 cases develop beyond 2 years (time period not specified) for a total of 9.1% of the original study population.

HOW DO WE SCREEN FOR CTEPH?

Computed tomographic pulmonary angiography (CTPA) has become the standard diagnostic test for acute PE, and a good-quality CTPA that is negative for acute PE effectively rules the diagnosis out. Unlike for acute PE, though, CTPA is not a preferred diagnostic test for CTEPH. Instead, the ventilation/perfusion, or V/Q, scan is the preferred and recommended screening test for CTEPH.

Tunariu et al demonstrated that as a screening test for CTEPH, the V/Q scan had >96% sensitivity, meaning that a negative (ie, normal) V/Q scan essentially rules out the presence of CTEPH. Conversely, Tunariu et al also showed that CTPA had a sensitivity of only 51% as a screening test for CTEPH, with a falsely negative finding in 38 of 78 cases studied. Multiple national and international guidelines recommend the use of the V/Q scan as the CTEPH screening tool of choice.

The absence of prior acute PE does not exclude a diagnosis of CTEPH

Applying even the lower end of this range of estimates to the annual population of survivors of acute PE suggests there could be thousands of incident cases of CTEPH each year in the US. Further, though CTEPH is a complication of acute PE, as many as 25% to 30% of patients who have CTEPH may never have had an overt PE or a history suggestive of PE. The true incidence of CTEPH may, therefore, be underestimated, because postembolism observational studies do not include patients who have no history of venous thromboembolism.

As many as 1 in 25 survivors of acute PE (>3 months of anticoagulation) may go on to develop CTEPH within 2 years

If after 3 months of anticoagulation following an episode of acute PE a patient still has or develops such symptoms, CTEPH should be suspected and the patient referred to a PH specialist who can perform CTEPH screening.

This adverstorial is brought to you by Bayer
confined to very distal segmental or subsegmental pulmonary arteries.4,24 The V/Q scan has many attributes that contribute to its utility as a screening tool for CTEPH.4 It is easy to read—suspected perfusion defects, regardless of origin, are readily recognizable. VQ scan monitoring also requires less radiation exposure than CTPA, and it avoids complications from administration of IV contrast. Finally, it offers a lower likelihood of incidental findings. Many patients who have been diagnosed with pulmonary arterial hypertension (PAH) have never had a V/Q scan to rule out potentially curable CTEPH. Findings from the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QERI, N=786) demonstrated that 43% of patients who had been diagnosed with PAH had been so diagnosed despite never having received a V/Q scan to screen for, and potentially rule out, CTEPH.25 This finding suggests that patients who have been previously diagnosed with PAH without having had a V/Q scan and who are not meeting their PAH treatment goals should receive a V/Q scan to screen for CTEPH.

To stress the importance of the V/Q scan as a screening tool for CTEPH, the World Symposium on Pulmonary Hypertension observed that “underutilization of V/Q scans in screening PH invites potential misdiagnosis of PAH.”8 Such misdiagnosis can result in delay of assessment for potentially curative surgery for CTEPH.4,26-28 If V/Q scanning is not readily available, the patient should be referred to a center that can perform a V/Q scan.

**CONFIRMATION OF CTEPH DIAGNOSIS**

An abnormal V/Q scan showing perfusion defects is not enough on its own to diagnose CTEPH. To confirm CTEPH, right heart catheterization (RHC) must be performed to confirm mean PAP ≥25 mmHg, with pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Selective pulmonary angiography is typically used to confirm presence of CTEPH lesions.4 CTPA and magnetic resonance angiography can contribute complementary information on the lesions, their surroundings, and their accessibility.4,8

Once the diagnosis of CTEPH is confirmed, all CTEPH patients must be assessed for operability by an experienced CTEPH team that would plan, perform, and follow-up the patient’s surgery. Operability assessment must consider the patient’s risk, including quality of and accessibility of lesions, hemodynamic assessment, and consideration of comorbidities and patient characteristics.4,8 If one experienced CTEPH team determines that a patient has inoperable disease, a corroborating opinion from a second experienced CTEPH team should be secured, if possible.4 This is because operability assessment is subjective, and what may be deemed by one CTEPH team as inoperable disease may well be deemed operable by another experienced CTEPH team.

**CTEPH TREATMENT IN SURGICAL CANDIDATES: PULMONARY THROMBOEMBOLARCTOMY**

Referral of CTEPH patients to PH centers for confirmation of diagnosis, operability assessment, and comprehensive care is essential.4 Because it is potentially curative, PTE surgery is considered the first-line treatment of choice for patients diagnosed with CTEPH who are appropriate surgical candidates.8-10 Rather than reserving PTE surgery as a “last-ditch” treatment option, patients who have operable CTEPH should be referred for surgery without delay.4 Though all CTEPH patients require lifelong anticoagulation to prevent in situ pulmonary artery thrombosis and recurrent venous thromboembolism,4 anticoagulation is not sufficient to treat the progressive right ventricular dysfunction that results from CTEPH. PTE surgery allows for the removal of central obstructing lesions, resulting in improvement and often normalization of pulmonary hemodynamics.4 About two-thirds of patients have normal hemodynamics following PTE.27

**REFERENCES**


 based on a study with 223 patients in which 3.8% were diagnosed with CTEPH within 2 years of their first episode of pulmonary embolism with or without prior deep-vein thrombosis (95% CI, 1.1 to 6.5).4

**VISIT scan4CTEPH.com FOR MORE INFORMATION**
Surveillance program IDs enterovirus early

BY DEEPAK CHITNIS
Frontline Medical News

ATLANTA – Implementing surveillance programs at area hospitals is an effective tool for health care providers and public health officials to identify severe acute respiratory illness (SARI) and enterovirus specifically early.

“We do surveillance for respiratory illness [at] three sentinel sites that participate in the Minneapolis-St. Paul metro area,” explained Hannah Friedlander, an epidemiologist with the Minnesota Department of Health in St. Paul, who presented the study. “[But] our surveillance didn’t actually actively look for enterovirus, it looked for rhinovirus, which is known to cross-react with enterovirus on PCRs [polymerase chain reactions],” she said at the International Conference on Emerging Infectious Diseases.

To remedy that, the surveillance program – which involves the participation of one pediatric hospital, one hospital serving both children and adults, and one primarily serving adults – added testing for enterovirus to PCRs of all SARI specimens collected from Sept. 1 through Oct. 31, 2014. In total, 363 SARI specimens were collected over that time frame, of which 100 (28%) were found to be pan-EV positive and underwent further evaluation for EV-D68. Ultimately, 64 of the EV-positive specimens were found to be EV-D68 strains.

The vast majority of cases identified as being caused by the EV-D68 strain (73%) were collected between Sept. 6 and Sept. 20. This indicates that starting surveillance of SARI cases when enteroviruses traditionally become more frequent could allow for faster determination of which strain is most prevalent and what the optimal treatment should be. “It’s hard to say if this was surprising because we hadn’t previously been looking for enterovirus, so we don’t have another year to compare [these] data to,” Ms. Friedlander explained. “But I think it’s surprising that we saw as much of [enterovirus] as we did.”

Most cases of EV-D68 (64, or 36%) were in patients between the ages of 5 and 11 years, with a median age of 6 years. A total of 52 (81%) EV-D68 cases presented with shortness of breath, and 31 cases (48%) presented with wheezing or cough. Hospital stays of 4 days or fewer occurred in 73% of cases, with a median stay length of 3 days; 33% of EV-D68 patients required admittance to the ICU, and 13% of EV-D68 patients were placed on a mechanical ventilator at some point during treatment.

“This fall is our third year doing this type of surveillance, so at the time the data for this [were] collected, we only had 1 year of surveillance under our belt,” she explained. “We now look prospectively for enterovirus, not EV-D68 specifically, so it’ll be interesting to see as the years go on if this was an outlier year.”

Ms. Friedlander and her coinvestigators implore hospital systems to not only have surveillance programs in place, but also for them to have the flexibility to include additional testing should the need for it arise. That flexibility is what proved crucial in the early identification of EV-D68 in her own study population.

This study was funded by the Council of State and Territorial Epidemiologists, and the Centers for the Disease Control and Prevention. Ms. Friedlander did not report any relevant financial disclosures.

dchitnis@frontlinemedcom.com

USPSTF: Ask about smoking, urge quitting

BY KATIE WAGNER LENNON
Frontline Medical News

The U.S. Preventive Services Task Force has issued a final, grade A recommendation calling on all clinicians to ask all adults whether they smoke, advise them to quit if they do, and provide cessation aids to adults who use tobacco.

The guideline also includes two grade 1 (insufficient evidence) statements, one on the balance of benefits versus harms of pharmacotherapy interventions for tobacco cessation in pregnant women and the other on electronic nicotine delivery systems for tobacco cessation in all adults (Ann Intern Med. 2015 Sep 22. doi: 10.7326/M15-2023).

The guideline reaffirms the 2009 USPSTF recommendation, which urges clinicians to ask all adults about tobacco use and provides tobacco cessation interventions to help them quit.

The new recommendations differ from the 2009 recommendation in that it calls for more evidence on the use of e-cigarettes for smoking cessation in adults and the use of medications to help pregnant women stop smoking.

“A large body of evidence on interventions for smoking cessation already exists, and the overall benefit of pharmacotherapy and behavioral counseling to promote smoking is well established,” according to the recommendations.

“Tobacco is the leading preventable cause of disease, disability, and death in the United States,” with cigarette smoking, specifically, causing more than 480,000 premature deaths annually and accounting for one in every five deaths, according to the recommendations.

In pregnant women, smoking increases the risk of congenital anomalies; perinatal complications, such as preterm birth, fetal growth restriction, and placental abruption; miscarriage and stillbirth; and neonatal or pediatric complications, such as sudden infant death syndrome and impaired lung function in childhood,” the recommendations say.

According to a 2013 systematic review of 28 studies, rates of smoking abstinence at 6 months or more were 8% in groups that received physician advice, compared with 5% in groups that received no advice or usual care.

Pharmacotherapy was effective at stopping nonpregnant smokers from continuing to smoke; a 2012 systematic review of 117 nicotine replacement therapy (NRT) studies found that 17% of participants who took any form of an NRT drug abstained from smoking for 6 months or more, compared with 10% of participants who received placebo or did not take an NRT drug, the review says.

Combinations of behavioral counseling and pharmacotherapy for smoking cessation also were effective; “a 2012 good-quality systematic review” found the abstinence rate of participants who received combination pharmacotherapy and intensive behavioral counseling was 14.5%, at 6 months or more, compared with 8% among control participants who received “usual care, self-help materials, or brief advice on quitting (which was less intensive than the counseling or support given to the intervention groups).”

For pregnant women, “a good-quality systematic review of 86 studies done in 2013” found that behavioral interventions were effective at improving rates of smoking cessation.

Compared with control participants, pregnant women who received any type of behavioral intervention before the third trimester had higher cessation rates late in pregnancy.

Responding to public comments, USPSTF said that “both intervention types (pharmacotherapy and behavioral intervention) are effective and recommended,” with combinations of interventions being the most effective way to help patients to stop smoking.

Further research is still needed to elucidate specific features of complex behavioral counseling interventions, benefits of pharmacotherapy in specific populations [such as pregnant women and adults with mental health conditions], and the efficacy of newer technology-based interventions such as Internet-based programs, mobile or smartphone applications, and text-messaging programs.”

The document also called for investigations into the safety, benefits, and harms of electronic nicotine delivery systems.

The authors of the recommendations stated they had nothing to disclose.

klennon@frontlinemedcom.com
Hypothyroidism associated with IPF mortality

BY AMY KARON
Frontline Medical News
FROM CHEST

Hypothyroidism affected almost 17% of patients with idiopathic pulmonary fibrosis and was independently associated with their mortality, according to a report in the September issue of CHEST.

“We report, to our knowledge for the first time, an association between hypothyroidism and idiopathic pulmonary fibrosis,” wrote Dr. Justin Oldham of the pulmonary and critical care section of the University of Chicago and his associates. “Hypothyroidism, a largely autoimmune process, is common among patients with IPF and may represent an additional feature of autoimmunity in this patient population.” The retrospective study could not assess causality, but raises questions about whether autoimmune abnormalities contribute to or exacerbate IPF, and whether hypothyroidism and IPF share common underlying causes, the investigators said.

To explore the question, they studied 196 patients with IPF, with an equal number of age-and sex-matched controls with COPD (Chest 2015;148:692-700).

Nearly 17% of IPF patients – including 13% of women and 28% of men – reported using thyroid replacement therapy with no history of thyroidectomy or radioactive iodine ablation. In contrast, only 7% of COPD controls had a recorded diagnosis of hypothyroidism (odds ratio, 2.7; 95% confidence interval, 1.3-5.5; P = .01). Men and women with IPF and comorbid hypothyroidism had significantly shorter survival than did patients who had IPF only (P = .001). Hypothyroidism also independently predicted mortality in the multivariable analysis (hazard ratio, 2.1; 95% CI, 1.3-3.4), as did sequential increases in gender, smoking, and number of recorded hospitalizations.


Of all the things you recommend to protect your patients aged 65+

HERE’S ONE YOU CAN GET DONE TODAY

Make vaccination a priority.
Help protect your appropriate patients with Prevnar 13®.

• Pneumococcal pneumonia can have serious consequences and may lead to hospitalization
• The CDC’s ACIP recommends Prevnar 13® for adults aged 65+
• Prevnar 13® was shown to prevent pneumococcal pneumonia and IPD in a landmark efficacy trial of 84,496 adults aged 65+
• Prevnar 13® is covered by the Medicare Part B FFS benefit for adults aged 65+ with $0 in out-of-pocket costs

Learn more about Prevnar 13® and the information above at www.Prevnar13info.com

INDICATION
- In adults 50 years of age and older, Prevnar 13® is indicated for active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

LIMITATIONS OF USE AND EFFECTIVENESS
- Prevnar 13® will only help protect against S pneumoniae serotypes in the vaccine

IMPORTANT SAFETY INFORMATION
- Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid–containing vaccine is a contraindication
- Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response
- In adults, antibody responses to Prevnar 13® were diminished when given with inactivated trivalent influenza vaccine
- In adults, the commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle or joint pain, decreased appetite, chills, or rash

Please see Brief Summary of Prescribing Information on adjacent page(s).
Continued from previous page

age, and physiology (GAP) stage, the investigators said. “These clus- 
tions held when transplant-free, transplant-excluded, and transplant-
as-a-competing-event Cox regression models were con- 
trasted. Furthermore, multivariable

analyses of data from two IPF clini-
cal trials (ACE-IPF and PANTHER) revealed similar associations among 

hypothyroidism, GAP stage, and mortality, they said.

Exactly how hypothyroidism con- 
tributes to IPF and related mor-
tality is unclear, starting with its 

associates. Because the study did 
not examine longitudinal changes in 
thyroid stage, they could not relate 
those To IPF progression, they 

noted.

Although identified patients whose thyroid disease was known 

to not be autoimmune, they could

not specifically confirm that all re-

maining patients with hypothyroid-

ism had autoimmune thyroiditis,

because most had been diagnosed 

years before.

Future longitudinal studies should 

examine whether IPF and hypothy-

roidism share underlying causes, 

and should examine why hypothyroidism

seems to increase IPF-related mortal-

ity, they concluded.

22 PULMONARY MEDICINE • OCTOBER 2015 • CHEST PHYSICIAN

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Prevnar 13® is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

CONTRAINDICATIONS

Severe allergic reaction (eg, anaphylactic) to any component of Prevnar 13® or any diphtheria-containing vaccine.

WARNINGS AND PRECAUTIONS

The safety of Prevnar 13® was evaluated in 13 clinical trials in which 4729 infants and toddlers received at least 1 dose of Prevnar 13® and 2762 infants and toddlers received at least 1 dose of Prevnar® active control. Overall, the safety data show a similar proportion of Prevnar 13® and Prevnar® subjects reporting serious adverse events among US study subjects, a similar proportion of serious events occurring within 30 days post-vaccination, and a similar proportion of serious adverse events occurring within 1 month after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Adult Clinical Studies

The safety of Prevnar 13® in adults was assessed in 7 clinical studies (Studies 6-12) conducted in the US in individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with leukocyte dysfunction, HIV infection, malignancy, hematologic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced efficacy and increased adverse reaction rates due to immunosuppression.

Apothesis in Premature Infants

Adults and adolescents aged 18 years and older

The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred 0.8% among Prevnar 13® recipients and 3.9% among Prevenar 13® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevenar® reported earlier were: 0.3% to 1.3% during the first 30 days after vaccination; 3.5% to 3.7% from the bleed after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Infant Clinical Studies

The safety of Prevnar 13® was evaluated in 13 clinical trials in which 4729 infants and toddlers received at least 1 dose of Prevnar 13® and 2762 infants and toddlers received at least 1 dose of Prevnar® active control. Overall, the safety data show a similar proportion of Prevnar 13® and Prevnar® subjects reporting serious adverse events among US study subjects, a similar proportion of serious events occurring within 30 days post-vaccination, and a similar proportion of serious adverse events occurring within 1 month after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Infant Clinical Studies

The safety of Prevnar 13® in adults was assessed in 7 clinical studies (Studies 6-12) conducted in the US in individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with leukocyte dysfunction, HIV infection, malignancy, hematologic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced efficacy and increased adverse reaction rates due to immunosuppression.

Apothesis in Premature Infants

Adults and adolescents aged 18 years and older

The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred 0.8% among Prevnar 13® recipients and 3.9% among Prevenar 13® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevenar® reported earlier were: 0.3% to 1.3% during the first 30 days after vaccination; 3.5% to 3.7% from the bleed after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Infant Clinical Studies

The safety of Prevnar 13® in adults was assessed in 7 clinical studies (Studies 6-12) conducted in the US in individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with leukocyte dysfunction, HIV infection, malignancy, hematologic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced efficacy and increased adverse reaction rates due to immunosuppression.

Apothesis in Premature Infants

Adults and adolescents aged 18 years and older

The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred 0.8% among Prevnar 13® recipients and 3.9% among Prevenar 13® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevenar® reported earlier were: 0.3% to 1.3% during the first 30 days after vaccination; 3.5% to 3.7% from the bleed after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Infant Clinical Studies

The safety of Prevnar 13® in adults was assessed in 7 clinical studies (Studies 6-12) conducted in the US in individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with leukocyte dysfunction, HIV infection, malignancy, hematologic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced efficacy and increased adverse reaction rates due to immunosuppression.

Apothesis in Premature Infants

Adults and adolescents aged 18 years and older

The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred 0.8% among Prevnar 13® recipients and 3.9% among Prevenar 13® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevenar® reported earlier were: 0.3% to 1.3% during the first 30 days after vaccination; 3.5% to 3.7% from the bleed after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.

Solicited Adverse Reactions in Infant Clinical Studies

The safety of Prevnar 13® in adults was assessed in 7 clinical studies (Studies 6-12) conducted in the US in individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with leukocyte dysfunction, HIV infection, malignancy, hematologic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced efficacy and increased adverse reaction rates due to immunosuppression.

Apothesis in Premature Infants

Adults and adolescents aged 18 years and older

The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred 0.8% among Prevnar 13® recipients and 3.9% among Prevenar 13® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevenar® reported earlier were: 0.3% to 1.3% during the first 30 days after vaccination; 3.5% to 3.7% from the bleed after the infant series; 2.3% and 2.9% from the bleed after the infant series; 1.9% and 2.1% from the vaccine after the toddler series; and 0.4% and 0.3% from the vaccine after the toddler series. These data do not provide evidence for a possible relationship between the occurrence of serious adverse events and administration of Prevnar 13®.
IASLC aims to reduce smoking, lung cancer

BY SUSAN LONDON
Frontline Medical News

DENVER – The International Association for the Study of Lung Cancer released an updated Tobacco Control and Smoking Cessation declaration that outlines a set of measures aimed at reducing smoking and lung cancer.

The declaration could be viewed as a vaccine of sorts, according to Kenneth Michael Cummings, Ph.D., a professor at the Hollings Cancer Center, Medical University of South Carolina, and co-chair of IASLC’s Tobacco Control and Smoking Cessation Committee.

“How about a vaccine to prevent 80% of lung cancer deaths worldwide? We have it: Get rid of tobacco,” he said in a press conference at the World Congress on Lung Cancer, where the declaration was released.

The previous declaration, released in 2008, focused heavily on giving the Food and Drug Administration the authority to regulate tobacco in the United States, which it now has. Since then, the economics of tobacco have evolved rapidly, and new products such as e-cigarettes have become available.

Also, 180 countries have ratified the World Health Organization’s Framework Convention on Tobacco Control (FCTC) treaty, allowing them to implement evidence-based policies such as smoke-free environments, warning labels, advertising bans, and taxation.

Nevertheless, lung cancer still accounts for nearly 2 million cases and 1.6 million lives lost each year. And at least 80% of those deaths are directly attributable to smoking, Dr. Cummings said.

In some parts of the world, cigarette consumption has declined, but “that’s not happening everywhere,” he said. “In parts of Asia, such as China, Japan, and Southeast Asia, and in Latin America, we are still seeing a rapid increase in lung cancer deaths. And in parts of the world which have not taken up smoking but are the targets of the industry, such as Africa and Indonesia, we are likely going to see an epidemic there, which can be prevented, which is really the point of our new statement.”

The 2015 declaration has five components that address tobacco control and smoking cessation.

The first component calls for forceful implementation of the FCTC treaty, especially through higher cigarette prices via taxation. “This is…the most important component of our vaccine, for every member of this organization to really advocate for raising the cigarette prices to a level where it makes it unaffordable for young people to take up the behavior,” Dr. Cummings said. In low- and middle-income countries, where cigarettes remain relatively inexpensive, imposing a tax of at least 70% of the retail price would immediately cut consumption by about a third (N Engl J Med. 2014;370:60-8).

Trade policies and tobacco interference are related issues, he noted. “Our organization has been strong in trying to keep tobacco out of trade agreements.” Some countries, such as Malaysia, have refused to allow tobacco to be part of the Trans-Pacific Partnership agreement now under negotiation. “We need to support that [stance] because if tobacco is in there, we have countries being sued under trade agreements for doing the right things in terms of implementing policies.”

The declaration’s second component calls for holding cigarette companies civilly and criminally accountable for their actions. While Philip Morris International has stated that it supports evidence-based regulation of tobacco, “I think our organization can help [by taking] cigarettes off the shelf today,” Dr. Cummings said. Holding manufacturers accountable in courts is another way to raise the price of cigarettes and thereby reduce consumption, he added.

The third component of the declaration is to support policies that keep young people from starting to smoke, such as raising the legal age of use to 21. “The neurobiology is very clear: The younger you are when you get exposed to an addictive substance, the more likely it is you are going to find it hard to quit at the end. So, raising the legal age is certainly something we ought to do,” Dr. Cummings asserted, adding that 21 “is sort of a compromise” as the brain continues to develop until the age of 25.

Ensuring provision of tobacco-cessation services to all smokers, the declaration’s fourth component, is important no matter a patient’s status. “Even in our cancer patients, it’s not too late. It has a big effect on their outcomes,” he said.

The fifth component is support for policies that address alternatives for nicotine delivery that are likely safer than cigarettes. “I don’t really care if companies make money selling something, but they don’t have to kill one out of two of their consumers to do it,” Dr. Cummings commented.

These alternatives might include e-cigarettes, provided evidence supports their inclusion. “I think that’s the problem we have with e-cigarettes today,” he said, noting that much less is known about them as compared with standard cigarettes, and that the products and manufacturers change monthly.

Mandates raise flu shot uptake in health care setting

BY MIKE BOCK
Frontline Medical News

Overall, 77% of health care personnel reported receiving an influenza vaccination during the 2014-2015 season, with the highest vaccination coverage reported in work sites with employer requirements for vaccination, according to an investigation published in the Morbidity and Mortality Weekly Report (2015 Sep 18;64[36]:993-9).

Vaccination data came from an opt-in Internet panel survey conducted by Abt Associates for the Centers for Disease Control and Prevention, and included questions on demographic characteristics, occupation, work setting, self-reported influenza vaccination, and employer vaccination policies. Results from 1,914 survey responses were analyzed. The overall health care personnel influenza vaccination coverage estimate for the 2014-2015 season was 77%, compared with 75% for the 2013-2014 season. When compared with the 2013-2014 season, coverage in 2014-2015 was higher among pharmacists (95% vs. 86%), assistants/aides (64% vs. 58%), and nonclinical personnel (75% vs. 69%). Coverage among other clinical personnel decreased from 87% in 2013-2014 to 81% in 2014-2015, while other categories experienced little change between the two time periods.

The researchers, led by Carla L. Black, Ph.D., of the National Center for Immunization and Respiratory Diseases, CDC, noted that among health care personnel whose employers did not require vaccination, coverage among those whose employer made vaccination available on-site at no cost for more than 1 day was 84%, compared with 74% among those whose employer made vaccination available at no cost for 1 day only, and 60% among those whose employer did not provide influenza vaccination on-site at no cost but instead actively promoted vaccination through other mechanisms.

“These findings support recommendations for a comprehensive strategy that includes easy access to vaccination at no cost on multiple days, along with promotion of vaccination, to increase [health care personnel] influenza vaccination coverage,” Dr. Black and her colleagues wrote.

mbock@frontlinemedcom.com
For the long-term, once-daily, maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD)

Prescribe INCRUSE ELLIPTA
one inhalation, once daily

& help patients add more breath to their day

Indication
- INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Safety Information for INCRUSE ELLIPTA

CONTRAINDICATIONS
- The use of INCRUSE ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have hypersensitivity to umeclidinium or any of the excipients.

WARNINGS AND PRECAUTIONS
- INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta,-agonist.
- If paradoxical bronchospasm occurs, discontinue INCRUSE ELLIPTA and institute alternative therapy.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician 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 physician immediately if signs or symptoms of urinary retention develop.

ADVERSE REACTIONS
- The most common adverse reactions (≥1% and more common than placebo) reported in one 12-week and one 24-week clinical trial with INCRUSE ELLIPTA (and placebo) were: nasopharyngitis, 8% (7%); upper respiratory tract infection, 5% (4%); pharyngitis, 1% (<1); viral upper respiratory tract infection, 1% (<1%); cough, 3% (2%); arthralgia, 2% (1%); myalgia, 1% (<1%); upper abdominal pain, 1% (<1%); toothache, 1% (<1%); contusion, 1% (<1%); tachycardia, 1% (<1%). Other adverse reactions with INCRUSE ELLIPTA observed with an incidence <1% but more common than placebo included atrial fibrillation.
Provided improvement in health-related quality of life as measured by the St. George’s Respiratory Questionnaire (SGRQ)

- In the same 6-month study, INCRUSE ELLIPTA demonstrated an improvement in health-related quality of life, as measured by a decrease in mean SGRQ total score of 4.69 units, compared with placebo at Day 168
- The proportion of patients with a clinically meaningful decrease (defined as a decrease of at least 4 units from baseline) at Week 24 was greater for INCRUSE ELLIPTA (42%; 172/410) compared with placebo (31%; 86/274)
- These endpoints were not adjusted for multiple comparisons
- The SGRQ is a respiratory disease-specific, patient-reported instrument that measures symptoms, activities, and impact on daily life

Important Safety Information for INCRUSE ELLIPTA (cont’d)

ADVERSE REACTIONS (cont’d)

- In addition to the two placebo-controlled clinical trials with INCRUSE ELLIPTA, a 12-month trial evaluated the safety ofumeclidinium 125 mcg in subjects with COPD. Adverse reactions (incidence ≥1% and exceeded that in placebo) in subjects receiving umeclidinium 125 mcg were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

DRUG INTERACTIONS

- Avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.


INCRUSE® ELLIPTA®
(umeclidinium 62.5 mcg inhalation powder)
INCRUSE® ELLIPTA®
(umeclidinium inhalation powder)

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

1 INDICATIONS AND USAGE
INCRUSE ELLIPTA is an anticholinergic 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.

4 CONTRAINDICATIONS
The use of INCRUSE ELLIPTA is contraindicated in the following conditions: severe hypersensitivity to milk proteins or hypersensitivity to umeclidinium or any of the excipients [see Warnings and Precautions (5.3), Description (11)] of full prescribing information.

5 WARNINGS AND PRECAUTIONS
5.1 Deterioration of Disease and Acute Episodes
INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. INCRUSE ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of INCRUSE ELLIPTA in this setting is not appropriate. INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. INCRUSE ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INCRUSE ELLIPTA 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 INCRUSE ELLIPTA beyond the recommended dose is not appropriate in this situation.

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

5.3 Hypersensitivity Reactions
Hypersensitivity reactions may occur after administration of INCRUSE ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use INCRUSE ELLIPTA [see Contraindications (4)].

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

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

6 ADVERSE REACTIONS
The following adverse reactions are described in greater detail in other sections:
- Paradoxical bronchospasm [see Warnings and Precautions (5.2)]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.4)]
- Worsening of urinary retention [see Warnings and Precautions (5.5)]

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

A total of 1,663 subjects with COPD across 8 clinical trials (mean age: 62.7 years; 89% white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind, placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to 52 weeks [see Clinical Studies (14) of full prescribing information]. The incidence of adverse reactions associated with INCRUSE ELLIPTA in Table 1 is based upon 2 placebo-controlled efficacy trials: one 12-week trial and one 24-week trial.

Table 1. Adverse Reactions With INCRUSE ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INCRUSE ELLIPTA (n = 487)</th>
<th>Placebo (n = 348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Toothache</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than 1% but more common than placebo included atrial fibrillation. In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109 placebo) were treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the efficacy trials described above. Adverse reactions that occurred with a frequency greater than or equal to 1% in subjects
receiving umeclidinium 125 mcg that exceeded that in placebo in this trial were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rinitis, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

7 DRUG INTERACTIONS

7.1 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions (5.4, 5.5), Adverse Reactions (6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of human response, INCRUSE ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking INCRUSE ELLIPTA.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of INCRUSE ELLIPTA during labor and delivery. INCRUSE ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

It is not known whether INCRUSE ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when INCRUSE ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of INCRUSE ELLIPTA by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue INCRUSE ELLIPTA, taking into account the importance of INCRUSE ELLIPTA to the mother. Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

8.4 Pediatric Use

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

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of INCRUSE ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of INCRUSE ELLIPTA included 810 subjects aged 65 years and older, and, of those, 183 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C\text{max} or AUC, nor did protein binding differ between subjects with severe hepatic impairment and their healthy controls. No dosage adjustment is required in patients with renal impairment [see Clinical Pharmacology (12.3) of full prescribing information].

8.7 Renal Impairment

Patients with severe renal impairment (creatinine clearance less than 30 mL/min) showed no relevant increases in C\text{max} or AUC, nor did protein binding differ between subjects with severe renal impairment and their healthy controls. No dosage adjustment is required in patients with renal impairment [see Clinical Pharmacology (12.3) of full prescribing information].

10 OVERDOSE

No case of overdose has been reported with INCRUSE ELLIPTA. High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD. Treatment of overdose consists of discontinuation of INCRUSE ELLIPTA together with institution of appropriate symptomatic and/or supportive therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day (male/female, respectively) (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively). Umeclidinium tested negative in the following genotoxicity assays: the in vitro Ames assay, in vitro mouse lymphoma assay, and in vivo rat bone marrow micronucleus assay. No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

17 PATIENT COUNSELING INFORMATION

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

Not for Acute Symptoms: Inform patients that INCRUSE ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

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

• Symptoms get worse
• Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with INCRUSE ELLIPTA without physician/ provider guidance since symptoms may recur after discontinuation.

Paradoxical Bronchospasm: As with other inhaled medicines, INCRUSE ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue INCRUSE ELLIPTA.

Worsening of Narrow-Angle Glaucoma: Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a 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 (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develop.

INCRUSE and ELLIPTA are registered trademarks of the GSK group of companies.
Flu shots decrease severity, duration of illness

BY DEEPAK CHITNIS
Frontline Medical News

ATLANTA – Individuals who neglect to get their annual influenza vaccinations will likely experience more-severe symptoms and a longer duration of the illness if they contract the disease, specifically the A/H1N1 strain.

In a study of 155 influenza patients between 2009 and 2014, 138 (89%) were positive for influenza A virus, 111 (72%) of whom were vaccinated against influenza.

“We know that flu vaccines are about 60% effective, but of that remaining 40%, do they still get severe flu?” asked Dr. Eugene V. Millar of the Uniformed Services University of the Health Sciences in Bethesda, Md.

Sixty-six (48%) individuals contracted the A/H1N1 strain of the influenza virus; of these patients, those who had not received vaccination reported higher average severity scores for upper respiratory symptoms (7 vs. 3), lower respiratory symptoms (7 vs. 3), systemic symptoms (9.5 vs. 6), and total symptoms (22 vs. 12) than did subjects who did get vaccinated (P less than .01). “People ask me all the time why I bother getting a flu vaccine if it never works,” Dr. Millar said at the International Conference on Emerging Infectious Diseases.

“I tell them that if you’re walking around and talking to people, then it did work, even if you feel a little lousy; if you didn’t get that vaccination, you’d be on your back,” he continued.

Such disparity in the severity and duration of symptoms was not noted in 69 (50%) of the 135 influenza patients who contracted the A/H3N2 strain of the virus, nor in the 3 (2%) subjects who had an “untyped” form of influenza A. However, Dr. Millar cautioned that results regarding H3N2 may have been confounded by a couple of factors.

“As we’ve seen with the [H1N1] pandemic, it was just a pandemic of the snifflies, so it’s very hard to assess symptom severity when the differences are moderate to none,” Dr. Millar explained, adding that the variant strain of H3N2, which became prevalent during the 2014-2015 respiratory season proved to be the far more severe disease.

Furthermore, patients found with A/H1N1 were more likely to be put on antivirals, making it impossible to look at vaccine effect. In total, 884 patients with influenza-like illness were screened for inclusion in the study, from which the sample of 155 subjects was eventually derived.

Median age of the 155 subjects was 30.6 (P = .61), mean body mass index was 27.6 kg/m² (P = .07), males outnumbered females 88 to 67, and 106 subjects were active-duty military at the time they had influenza.

“These are healthy people presenting to outpatient clinics, it’s very interesting to see if the same thing would hold true for the elderly or people with underlying medical conditions, since those are the people we’re really trying to protect not only from influenza, but its complications, as well, such as secondary bacterial pneumonia,” Dr. Millar said.

Nine subjects (6%) had influenza during the 2009-2010 season, 36 (30%) were sick during the 2010-2011 season, 16 (10%) had influenza during the 2011-2012 season, 38 (25%) were sick during the 2012-2013 season, and 36 got the flu (23%) during the 2013-2014 season.

“’If you didn’t get that vaccination, you’d be on your back.’”

DR. MILLAR

Population-level data support flu vaccine recs

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Expanded influenza vaccination coverage among children between 2002 and 2012 appears to have provided direct benefit with respect to influenza-related hospitalizations among vaccinated children, according to an analysis of vaccination and hospitalization data.

Additionally, the coverage among children appears to have provided indirect benefits in adults. Cecile Viboud, Ph.D., of the National Institutes of Health, Bethesda, Md., reported at the International Conference on Emerging Infectious Diseases.

Between 2006-2007 and 2010-2011, the Advisory Committee on Immunization Practices (ACIP) broadened vaccination recommendations to include not only children aged 6-23 months, but also those aged 24-59 months, then those aged 5-18 years, and eventually all those over age 6 months. Consequently, the vaccine coverage rate increased from less than 5% in 2002 to about 52% in 2012 (and to about 70% in those under age 5 years).

“Modeling of weekly influenza-related hospitalization outcomes (pneumonia and influenza outcomes and respiratory and circulatory outcomes) provided solid evidence of a direct and significant protective effect of vaccination both in children under age 5 years and in those aged 5-19 years. This finding was consistent across disease outcomes and remained significant in those under age 5 after adjusting for state, but the association was weaker with stratification by season, Dr. Viboud noted.

Further, hospitalization rates among working-age adults and seniors aged 65-74 years declined with increasing pediatric vaccine coverage, suggesting an indirect protective effect that population, she said, noting that the vaccination rate among older adults remained stable across the study period.

No evidence was seen for an indirect protective effect among adults over age 74 years, she said.

Dr. Viboud and her colleagues used age-specific annual vaccination rates derived from the National Immunization Survey and the Behavioral Risk Factor Surveillance System.

Age-specific rates of influenza-associated hospitalizations were estimated for each season during 1989-2012 by modeling weekly pneumonia and influenza outcomes plus respiratory and circulatory outcomes from the State Inpatient Databases of the Agency for Healthcare Research & Quality.

“In a nutshell, we see strong statistical evidence for the direct protective effects of the influenza vaccination program in children on the basis of analyses of population-level hospitalization data, which supports the expansion of the ACIP flu vaccine recommendations in the past decade,” Dr. Viboud said in an interview. “We also find weak evidence of herd immunity effects, whereby hospitalization rates are reduced in adults. That the evidence is weak is perhaps not surprising given that vaccine uptake in children remains moderate (60% in most highly vaccinated states) and vaccine effectiveness is modest at 40%-60% depending on the season.”

The indirect effects may become clearer with increasing vaccine uptake, she added.

sworcester@frontlinemed.com
Surveillance data uphold early flu vaccination

BY SHARON WORCESTER
Frontline Medical News

ATLANTA – Influenza vaccine effectiveness during the 2010-2011 through 2013-2014 flu seasons was moderate for up to 6 months post vaccination – about the duration of the average flu season, according to surveillance data.

Vaccine effectiveness in 1,720 non–active-duty U.S. Department of Defense beneficiaries ranged from 40% to 69% across the flu seasons, and after adjusting for age group, calendar season, and flu season, significant and fairly consistent protection was provided for up to 180 days, Dr. Jennifer M. Radin and her colleagues at the Naval Health Research Center, San Diego, reported in a poster at the International Conference on Emerging Infectious Diseases.

The adjusted vaccine effectiveness was 61% during the first 2 weeks after vaccination, 62% from days 15 through 90, and 60% during days 91 through 180. After that, the effectiveness dropped to ~11%, they said.

Vaccine effectiveness in this study was assessed using outpatient febrile respiratory illness surveillance among a convenience sample of individuals of all ages, 75% of whom were under age 25 years, who presented with fever, cough, or sore throat at outpatient facilities in California and Illinois. Case patients were those who tested polymerase chain reaction–positive for influenza; those who were PCR negative for influenza served as controls.

“Previous studies have found that protection from contracting influenza declines over time following influenza vaccination due to decreasing antibody levels. However, we found... moderate, sustained protection up to 6 months post vaccination,” Dr. Radin said in a statement, explaining that at this level of effectiveness, vaccination reduces the risk of a doctor’s visit by 50%-70%.

The findings suggest that vaccine administration close to the start of flu season is associated with slightly increased vaccine effectiveness, but the start of flu season varies each year, thus optimal timing is hard to predict.

“Consequently, early flu vaccination may still offer the best overall protection,” Dr. Radin and her colleagues wrote. The finding of a dramatic drop in effectiveness after 6 months also underscores the importance of yearly vaccination.

sworcester@frontlinemedcom.com
**Asthma exacerbations seen often after meds stopped**

**The totality of the evidence demonstrates that OFEV slows IPF progression**

The totality of the evidence demonstrates that OFEV slows IPF progression. Two trials demonstrated significant reductions in the annual rate of forced vital capacity (FVC) decline compared with placebo. The INPULSIS®-1 (Study 2) trial showed a 52% relative reduction in the annual rate of FVC decline compared with placebo (-60 mL/year vs. -115 mL/year, respectively; P<.001, 95% CI=27, 173). The INPULSIS®-2 (Study 3) trial showed a 45% relative reduction in the annual rate of FVC decline compared with placebo (-207 mL/year vs. -300 mL/year, respectively; P<.001, 95% CI=45, 143).

**TOMORROW (Study 1):** OFEV demonstrated a 68% relative reduction in the annual rate of FVC decline compared with placebo (-60 mL/year vs. -191 mL/year, respectively; P<.01, 95% CI=78, 173).

**Gastrointestinal Disorders**

**Diarrhea**
- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients.
- Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. 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 diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV.

**Nausea 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. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients.
- For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. 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.

**Embryofetal Toxicity**
- OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.
Diarrhea was reported in 62% of patients receiving OFEV vs 18% on placebo.

Diarrhea can be managed by symptomatic treatment, dose reduction, or treatment interruption until diarrhea resolves to levels that allow continuation of therapy. If severe diarrhea persists despite symptomatic treatment, discontinue OFEV.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT’D)

Arterial Thromboembolic Events
- Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% 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 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
- Based on the mechanism of action (VEGFR inhibition), 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. 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 the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. 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.

Please see additional Important Safety Information and brief summary for OFEV on the following pages.
Continued from previous page

In addition, study participants who were women, were black, were younger than 19 years old, had a Charlson comorbidity index greater than or equal to 1, and had at least two outpatient visits for asthma were significantly associated with a shorter interval to asthma exacerbation (P less than .001 for all variables).

Finally, most study participants had a hospital or ED visit, systemic corticosteroids, two rescue inhalers in a 4-month period, or needed to return to baseline asthma controller treatment. The authors suggest that this is evidence that most of the cohort continued to have underlying asthma during the 2-year study period.

Furthermore, 33% of patients with less than 4 months of stability required return to baseline treatment versus 8%, 13%, and 15% for more than 12 months of stability, 8-11 months, and 4-7 months, respectively. Among the limitations noted by the authors: Data were from insured patients, data did not indicate if step-

**OFEV is only available through participating specialty pharmacies**

**TO GET YOUR APPROPRIATE PATIENTS WITH IPF STARTED ON OFEV:**

- **CONDUCT** liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)
- **COMPLETE** the OFEV Prescription Form—available at [www.hcp.OFEV.com](http://www.hcp.OFEV.com)—and fax it to one of the participating specialty pharmacies
- **OFFER** enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

**IMPORTANT SAFETY INFORMATION**

**ADVERSE REACTIONS**

- Adverse reactions reported in ≥5% of patients treated with OFEV and more commonly than in patients treated with placebo included diarrhea (62% vs. 18%), nausea (24% vs. 7%), abdominal pain (15% vs. 6%), liver enzyme elevation (14% vs. 3%), vomiting (12% vs. 3%), decreased appetite (11% vs. 9%), weight decreased (10% vs. 3%), headache (8% vs 5%), and hypertension (5% vs. 4%).
- The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (7.2% vs. 0.8%) and myocardial infarction (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 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-treated patients and 1.8% of placebo-treated patients.

**DRUG INTERACTIONS**

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers**
  
  - Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of potent P-gp and CYP3A4 inhibitors (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.

**USE IN SPECIFIC POPULATIONS**

**Nursing Mothers**

- Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Hepatic Impairment**

- Monitor for adverse reactions and consider dose modification or discontinuation of OFEV as needed for patients with mild hepatic impairment (Child Pugh A). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended.

**Smokers**

- Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

**Hepatic Impairment**

- Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Smokers**

- Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

**References:**


2. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014.


down involved consultation with a health care provider, and the cohort did not include patients who did not step down as a comparison.

"Individuals and their providers can cautiously apply the data from this study to decisions about stepping down asthma medications. The novel insights from this analysis that contribute to this decision making process are considered to the length of stability prior to step-down and the rate of asthma exacerbations in the 24 months following step-down," they said. The study was funded by the Mayo Foundation for Medical Education and Research. The authors reported no disclosures.

**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 prior to initiating treatment with OFEV [see Warnings and Precautions]. Recommendation: The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of 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. **Dosage 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 resolves to levels that allow continued therapy. 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 a patient does not tolerate 100 mg twice daily, discontinuation treatment with OFEV [see Warnings and Precautions and Adverse Reactions]. Dose modifications or interruptions may be necessary for liver enzyme elevations. For alterations amino transferase (AST) or alanineaminotransferase (ALT) >3 times <5 times the upper limit of normal (ULN) without signs of severe liver damage, interruption or treatment may be reduced to OFEV 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily). [see Warnings and Precautions and Adverse Reactions]. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

**CONTRAINDICATIONS**: None

**WARNINGS AND PRECAUTIONS**: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with severe hepatic impairment [see Use in Specific Populations]. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (84%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN [see Use in Specific Populations]. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dose modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders**: Diarrhea: Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. [see Adverse Reactions]. In most patients, these events were of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dose modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Diarrhea treated at home in first signs with adequate hydration and electrolyte replacement (e.g., loperamide), and consider treatment interruption if diarrheic continues. 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 diarrhea persists despite symptomatic treatment, discontinuation treatment with OFEV (nintedanib) 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 diarrhea or vomiting does not resolve, discontinuation treatment with OFEV. **Emphysema Toxicity**: OFEV: can cause fatal hemorrhage when administered to a pregnant woman. Nintedanib was embryotoxic and embryofetal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis) in oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of 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 2.5% 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 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**: Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In post-marketing surveillance, arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients and 0.6% of placebo-treated patients. 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 the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue 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 greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations [see Warnings and Precautions]; Gastrointestinal Disorders [see Warnings and Precautions]; Embryofetal Toxicity [see Warnings and Precautions]; Arterial Thromboembolic Events [see Warnings and Precautions]; Risk of Bleeding [see Warnings and Precautions]; Gastrointestinal Perforation [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 1000 IPF patients treated with 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 (Studies 1 and 2) and 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 patients treated with placebo. 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 (nintedanib), more than placebo, were infections (1.2% vs. 0.8%), and myelodysplasia (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 neoplasm malignancy (0.3% vs. 0.0%), and myelodysplasia (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACCE) including MI, fatal events were 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 10% of OFEV-treated patients versus 11% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrea (11%). Adverse reactions leading to discontinued treatment were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and headache (3%). Discontinue OFEV in patients with an incidence of ≥25% and more frequent in the OFEV than placebo treatment group is listed in Table 1.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OFEV, 150 mg n=723</th>
<th>Placebo n=508</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>62% 18%</td>
<td>24% 7%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>24% 7%</td>
<td>15% 6%</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>13% 6%</td>
<td>26% 7%</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>5% 2%</td>
<td>5% 2%</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>1% 0%</td>
<td>2% 1%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>8% 5%</td>
<td>8% 5%</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>1% 0%</td>
<td>1% 0%</td>
</tr>
</tbody>
</table>

**DRUG INTERACTIONS**: P-glycoprotein (Pgp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and to a minor extent, CYP3A4. Coadministration with oral doses of a P-g and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 (inhibitors, e.g., erythromycin) with OFEV may increase exposure to nintedanib in ~2-fold. 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-g and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 (inhibitors, e.g., carbamazepine, phenytoin, and St. John’s wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. Anticoagulation: Nintedanib therapy is dependent on levels and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust...
OFEV is prescribed to patients who are 18 years and older to reduce the risk of disease progression in patients with idiopathic pulmonary fibrosis (IPF).
Inpatient mortality has dropped for pneumonia

BY RICHARD FRANKI
Prominent Medical News

Inpatient mortality for pneumonia, acute MI, heart failure, and stroke each fell significantly from 2002 to 2012, the Agency for Healthcare Research and Quality reported. Over that period, mortality among adults hospitalized with pneumonia went from 65 per 1,000 admissions to 35.8 per 1,000 for a drop of 45%—largest of the four high-volume conditions. Corresponding declines for the others were 41% for acute MI, 29% for heart failure, and 27% for stroke, the AHRQ noted. Since “death following discharge from a hospital is not reflected in these data,” the report said, measures of inpatient mortality “can reflect both improvements in health care and shifts in where end-of-life care takes place over time.”

The estimates in the report are based on data from the Nationwide Inpatient Sample (2002-2011) and State Inpatient Databases (2012).

Continued from previous page

Ohio, and her coauthors. Dried cannabis leaves were the most popular form of cannabis used in portable vaporizers, and hash oil was more commonly used with e-cigarettes than THC-infused wax (Pediatrics. 2013 Sept. 7. doi: 10.1542/peds.2013-1727).

While acknowledging that the results might be an underestimation of true figures because of the limitations of self-reporting, the authors said that further research is needed to determine whether e-cigarette use might serve as a gateway to cannabis use and the health impact of vaporized cannabis.

“At this time, the relative safety of using e-cigarettes for vaping cannabis versus smoking combustible cannabis is not well established,” Dr. Moran and her coauthors wrote. “However, a recent study indicated that adults who vaporize hash oil experience greater subjective tolerance and evidence of dependence compared with those smoking combustible cannabis.”

Cannabis consumed through e-cigarettes is challenging for parents, teachers, and police to detect because the device does not produce the characteristic pungent aroma of smoked cannabis, the researchers noted.

“As e-cigarettes and related devices continue to gain popularity among youth, it will be important to monitor rates of using these products to vaporize cannabis.”

When asked about the findings, Dr. Robert L. DuPont said in an interview that American drug markets are changing rapidly, making more drugs available through highly potent routes of administration such as vaporization.

“This effective and convenient way of delivering THC has much appeal, especially to youth, being new, cool, and smoke-free, as the rate of cannabis passes cigarettes for youth,” said Dr. DuPont, president of the Institute for Behavior and Health in Rockville, Md., and the first director of the National Institute on Drug Abuse.

The National Institutes of Health funded the study. No conflicts of interest were declared.

In EGFRevolution.com.

Lung cancer is the leading cause of cancer-related deaths both in the US and worldwide.1,2 For NSCLC EGFRevolution+ patients, the recommended first-line treatment is EGF tyrosine kinase inhibitors (TKIs).1

The majority of tumors will acquire EGFR TKI–resistance mutations

Despite initial high response rates with first-generation EGFR TKIs, many tumors will develop new mutations and become resistant.1 A major barrier to disease control is resistance to treatment. Resistance to first-generation TKIs will develop in most patients with EGFRevolution+ advanced NSCLC on a currently approved EGFR TKI.2

After disease progression, clinical guidelines recommend subsequent treatments including either continuing with an EGFR TKI therapy or beginning platinum-based chemotherapy.1

Nearly 2 out of 3 cases of progression with first-generation EGFR TKIs are related to the T790M mutation

In patients with NSCLC who are EGFRevolution+, T790M is an acquired mutation and has been identified as the most common mechanism of acquired resistance in nearly 2 out of 3 patients.1,2 Development of T790M mutation may confer resistance through several potential mechanisms, which may include3:

- Steric hindrance, which reduces receptor binding of reversible EGFR TKIs
- Increased binding affinity of EGF for ATP, resulting in reduced TKI potency

Discovering the cause of resistance

Patients should be monitored for radiologic or clinical progression. Tumors can also be assessed for molecular progression to additional acquired mutations.1,1,2 When patients with EGFRevolution+ status progress, prior to changing therapy, a biopsy is reasonable to identify mechanisms of acquired resistance, as stated in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).3

AstraZeneca is a leader in lung cancer research

AstraZeneca is conducting ongoing research to understand the science of the T790M mutation as a driver of resistance.
Adaptive servo-ventilation is not beneficial and may even be harmful for patients who have predominantly central sleep apnea accompanying heart failure with reduced ejection fraction, Dr. Martin R. Cowie reported at the annual congress of the European Society of Cardiology. The noninvasive therapy did control central sleep apnea in a large international randomized controlled trial, but nevertheless did not affect the composite endpoint of death from any cause, life-saving cardiovascular intervention, or unplanned hospitalization for worsening HF. Moreover, it unexpectedly raised the risk of cardiovascular death by 34%, and significantly increased all-cause mortality as well, said Dr. Cowie of Imperial College London.

Adaptive servo-ventilation delivers servo-controlled inspiratory pressure on top of expiratory positive airway pressure during sleep, to alleviate central sleep apnea. This form of sleep-disordered breathing, which may manifest as Cheyne-Stokes respiration in patients who have HF with reduced ejection fraction, is reported to affect up to 40% of this patient population. Its prevalence rises as the severity of HF increases, and it is an independent risk marker for poor prognosis and death in HF.

A recent trial showed that continuous positive airway pressure (CPAP) did not improve morbidity or mortality in patients who had HF with central sleep apnea, but suggested that a treatment that could reduce the apnea-hypopnea index (AHI) – the number of apnea or hypopnea events per hour of sleep – to below 15 might be effective. Adaptive servo-ventilation can accomplish this, and small studies and meta-analyses have shown that the treatment improves surrogate markers including plasma concentration of brain natriuretic peptide, left ventricular ejection fraction (LVEF), and functional outcomes in heart failure.

Dr. Cowie and his associates conducted the SERVE-HF trial, assessing the effect of adding adaptive servo-ventilation to guideline-based medical therapy on survival and cardiovascular outcomes. He presented the trial results at the meeting, and they were simultaneously published online (N Engl J Med. 2015 Sep 1 [doi: 10.1056/NEJMoai1506459]).

The industry-sponsored study comprised 1,325 patients aged 22 and older treated and followed at 91 medical centers for a median of 31 months (range, 0-80 months). They were randomly assigned to receive medical therapy plus adaptive servo-ventilation delivered through a face mask for at least 5 hours every night (666 intervention subjects) or medical therapy alone (659 control subjects).

Central sleep apnea was well controlled only in the intervention group. At 1 year, their mean AHI was 6.6 events per hour, and the oxygen desaturation index – the number of times per hour that the blood oxygen level dropped by 3 or more percentage points from baseline level – was 8.6.

Yet the primary composite endpoint was not significantly different between the two study groups: The rate of death from any cause, life-saving cardiovascular intervention, and unplanned hospitalization for worsening HF was 54.1% with adaptive servo-ventilation and 50.8% without it. The treatment also had no significant effect on a broad spectrum of secondary measures such as symptoms and quality of life. Six-minute walk distance gradually declined in both groups, but that decline was significantly more pronounced in the intervention group, the investigators said.

Even more worrisome was the significant increase in mortality associated with adaptive servo-ventilation. Cardiovascular mortality was 29.9% with the treatment, compared with 24.0% without it, for a hazard ratio of 1.34. All-cause mortality was 34.8% with the treatment and 29.3% without it, for an HR of 1.28.

The reason for this unexpected result is not yet known. One explanation is that central sleep apnea may be a compensatory mechanism with potentially beneficial effects in patients who have HF. Attenuating those effects with adaptive servo-ventilation may then have been detrimental. For example, central sleep apnea, and particularly Cheyne-Stokes breathing, may beneficially activate the respiratory muscles, increase sympathetic nervous system activity, induce hypercapnic acidosis, increase end-expiratory lung volume, and raise intrinsic positive airway pressure.

Another possibility is that applying positive airway pressure with adaptive servo-ventilation may impair cardiac function in at least a portion of patients who have HF by decreasing cardiac output and stroke volume during treatment.

ResMed, maker of the AutoSet adaptive servo-ventilator, sponsored SERVE-HF, which was also supported by the National Institute for Health Research and the National Institutes of Health. Dr. Cowie disclosed ties with Servier, Novartis, Pfizer, St. Jude Medical, Boston Scientific, Respircardia, Medtronic, and Bayer; his associates reported ties to numerous industry sources.

Oropharyngeal exercises significantly cut snoring

Eight minutes of oropharyngeal exercises performed three times a day significantly reduced snoring, according to a report in the September issue of CHEST.

At 3 months, the snore index and the total snore index dropped significantly for the exercise group but not the control group, said Vanessa Leito, Ph.D., of the Sleep Laboratory of the University of São Paulo in Brazil and her associates.

The regimen improved snoring symptoms among primary snorers as well as patients with mild to moderate obstructive sleep apnea, although the apnea-hypopnea index only improved among patients with moderate OSA, the researchers added.

After 3 months, the intervention group had significantly improved on both the snore index and the total snore index. The intervention group also improved significantly on perceived intensity and frequency of snoring.

“This set of oropharyngeal exercises is a promising treatment of large populations suffering from snoring who are currently largely ignored by the medical community,” they said.

Snoring is embarrassing and disruptive, and can exacerbate pharyngeal neurogenic lesions and carotid artery atherosclerosis, but few studies have objectively examined...
ined interventions for primary snorers or patients with mild OSA, the researchers said.

In their randomized trial of 39 such patients, the intervention group performed six oropharyngeal exercises three times daily while the control group patients practiced breathing exercises and wore nasal dilator strips at night. Both groups performed nasal lavage with saline solution three times a day.

Average age was 46 years, and mean body-mass index was 28.2 kg/m². A blinded researcher evaluated data from computerized polysomnography and a snoring recorder (Chest 2015;148:683-81).

Nasopharyngeal exercises used in the study were as follows:

- Push tip of tongue against hard palate and slide tongue backward (20 times).
- Suck entire tongue up against palate (20 times).
- Force back of tongue against floor of mouth while touching tip of tongue to bottom incisors (20 times).
- Elevate soft palate and uvula while intermittently saying ‘A’ (20 times).
- Place finger in mouth while pressing buccinator muscle outward (10 times per side).
- Chew and deglutinate on both sides of mouth whenever eating. Avoid perioral contraction.

After 3 months, the intervention group had significantly improved on both the snore index (snors per hour; \( P = .041 \) for change from baseline) and the total snore index (the total sound intensity of snors per hour; \( P = .033 \)), the researchers said. The intervention group also improved significantly on several subjective measures, including perceived intensity and frequency of snoring and sleep quality. The control group only improved in terms of subjective snore frequency, the researchers said.

The apnea-hypopnea index did not drop significantly for the overall intervention group, but did improve significantly among patients with moderate OSA, they added. “The most likely explanation is that a ‘floor effect’ in the AHI prevented the observation of any effect on this metric among patients with mild or no OSA at study entry,” Dr. Ieto and her associates said.

“Our results point out that snoring, rather than AHI, is probably the best metric to follow patients with mild forms of OSA in whom the most significant complaint is snoring,” they said.

The study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The researchers declared they had no competing interests.
Obstructive sleep apnea often complicates heart failure

BY MITCHEL L. ZOLER
Frontline Medical News

LONDON – The majority of patients with severe heart failure had sleep-disordered breathing and, in most affected patients, this manifested as obstructive sleep apnea, in an analysis of more than 1,000 German heart failure patients enrolled in a multicenter registry.

“The vast majority of heart failure patients with sleep-disordered breathing [SDB] have obstructive sleep apnea, which differs from previous results,” said Dr. Olaf Oldenburg at the annual congress of the European Society of Cardiology. Possible reasons why this German registry had different findings, compared with prior reports, were its inclusion of heart failure patients with milder symptoms, inclusion of patients with preserved ejection fraction, and in-
The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis.

The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection.

SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents.

Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma.

ECG changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT.

SYMBICORT is indicated for the treatment of asthma in patients 12 years and older (also see Boxed WARNING on front cover).

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

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection.

SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents.

Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma.

ECG changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. Use caution with the coadministration of SYMBICORT.

References:
3. Data on File, 3088224, AZPLP.
4. Data on File, 1084400, AZPLP.
5. 2015 Express Scripts Preferred Drug List.

Please see Brief Summary of full Prescribing Information, including boxed WARNING, on following pages.
The data he reported came from the Schlaef-HXT (Sleep Disordered Breathing in Heart Failure) registry, which enrolled patients with heart failure and reduced or preserved ejection fraction and any New York Heart Association functional class treated either at German hospitals or in physician offices. He reported data for 1,186 fully assessed and classified patients, who averaged 68 years old and two-thirds of whom were men. Slightly more than half had heart failure with reduced ejection fraction, and about half had New York Heart Association class II heart failure, a quarter had class III heart failure, with the remaining patients divided rough-
and the remaining 14% had either a
apnea, 22% had central sleep apnea, severe SDB (percentages total 101% 24% had no SDB, 37% had mild SBD, compared between patients with heart failure and preserved ejection fraction, who had a 36% prevalence of SDB requiring treatment. Moderate or se-
vere central sleep apnea occurred in 13% of patients with reduced ejection fraction and in 9% of patients with preserved ejection fraction.

A second report at the congress by Dr. Clinabre showed that the dura-
tion of time when a patient’s oxygen

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>SYMBICORT</th>
<th>Budicronate/formoterol</th>
<th>Formoterol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mcg</td>
<td>80/4.5 mcg</td>
<td>80/4.5 mcg</td>
<td>80/4.5 mcg</td>
<td>80/4.5 mcg</td>
</tr>
<tr>
<td>160 mcg</td>
<td>160/4.5 mcg</td>
<td>160/4.5 mcg</td>
<td>160/4.5 mcg</td>
<td>160/4.5 mcg</td>
</tr>
<tr>
<td>4.5 mg</td>
<td>4.5 mg</td>
<td>4.5 mg</td>
<td>4.5 mg</td>
<td>4.5 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SYMBICORT 160/4.5 mcg</th>
<th>SYMBICORT 80/4.5 mcg</th>
<th>Formoterol 4.5 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.7</td>
<td>1.1</td>
<td>2.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Postmarketing Experience**

The increased average duration of patient exposure to SYMBICORT patients should be taken into account, as incidences are not adjusted for in instances of treatment duration.

**Table 1. Adverse reactions occurring at an incidence of ≥2% more commonly in the SYMBICORT group.**

<table>
<thead>
<tr>
<th>Table 1. Adverse reactions occurring at an incidence of ≥2% more commonly in the SYMBICORT group.</th>
<th>SYMBICORT 80/4.5 mcg</th>
<th>SYMBICORT 160/4.5 mcg</th>
<th>Formoterol 4.5 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.7</td>
<td>1.1</td>
<td>2.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Table 2. Adverse reactions occurring at an incidence of ≥2% more commonly in the SYMBICORT group.**

<table>
<thead>
<tr>
<th>Table 2. Adverse reactions occurring at an incidence of ≥2% more commonly in the SYMBICORT group.</th>
<th>SYMBICORT 80/4.5 mcg</th>
<th>SYMBICORT 160/4.5 mcg</th>
<th>Formoterol 4.5 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.7</td>
<td>1.1</td>
<td>2.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3.5</td>
<td>4.3</td>
<td>3.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.7</td>
<td>3.5</td>
<td>2.6</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Nasopharyngitis**

Nasopharyngitis is a common adverse reaction, occurring in over 3% of patients treated with SYMBICORT. Clinical trials have shown that nasopharyngitis is more common in patients treated with SYMBICORT than with placebo. The most common symptom of nasopharyngitis is a sore throat, which may be associated with fever, cough, and fatigue. In clinical trials, nasopharyngitis was reported in 3% of patients treated with SYMBICORT and in 0.5% of patients treated with placebo. The symptoms of nasopharyngitis usually resolve within a few weeks without treatment. In some patients, nasopharyngitis may persist for several weeks. In rare cases, nasopharyngitis may be severe enough to require discontinuation of SYMBICORT. In general, nasopharyngitis is self-limiting and resolves without treatment.
More post-adenotonsillectomy in kids with OSA

In children who had adenotonsillectomy; children with obstructive sleep apnea (OSA) have nearly five times more respiratory complications after surgery than children with OSA, a multi-study review concluded.

Graziela De Luca Canto, Ph.D., of the Federal University of Santa Catarina, Brazil, and her associates performed a data review by identifying 1,254 citations found via electronic database searches; after eliminations, only 23 studies were included in the final analysis.

Although children with OSA have nearly five times more respiratory complications after adenotonsillectomy than their peers, their odds (odds ratio, 4.90), they are less likely to have post-operative bleeding, compared with children without OSA (OR, 0.41).

Among both groups, the most frequent complication was respiratory compromise (9.4%), followed by secondary hemorrhage (2.6%).

Because children with OSA may be more likely to require supplemental oxygen, oral or nasal airway insertion, or assisted ventilation in the immediate postoperative period than their peers, the authors suggested that anesthesiologists would be wise to screen patients for snoring, airway dysfunction, and other airway anatomic disorders before performing surgery.

Recent safety data show that SYMBICORT has not been conducted in patients with renal impairment.

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacodynamic studies, single doses of 105 mg (12 administrations of 8.8 mg) of budesonide were administered to pregnant rats and 115 mg (12 administrations of 10 mg) to pregnant rabbits. A total of 105 mg was 1250 mg (12 administrations of 85.4 mg) and 115 mg was administered as a single dose to both female subjects and patients who underwent a comprehensive sleep study with pulse oximetry measurement. Patients who undergo a comprehensive sleep study with pulse oximetry measurement following major surgery should be closely monitored.

Endocarditis

The potential for allergic-type effects following overdosage of budesonide is low. Following acute doses for prolonged periods, systemic corticosteroids such as hydrocortisone may occur (see WARNINGS AND PRECAUTIONS). In rabbits, a dose of 1 mg/kg of formoterol was administered for 3 weeks causing minimal dermatologic changes (4%). In studies in infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 1-10 weeks before the last menstrual period), the period when most major malformations occur. The dose of inhaled corticosteroids was similar to the general population (3% to 5% of the patients treated with SYMBICORT had a mcg/m² basis).

In controlled clinical studies there have been two mild corticosteroid incidences including budesonide; a component of SYMBICORT may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of the reduction in growth velocity associated with SYMBICORT use in children is not clearly known. The possibility that children who have undergone surgery and have a minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis). There were also instances of oral and intramuscular edema observed in rats. In studies in patients who underwent a comprehensive sleep study with pulse oximetry measurement. Patients who underwent a comprehensive sleep study with pulse oximetry measurement following major surgery should be closely monitored.

In a study of 1447 asthma patients 6 to 12 years of age, those treated with SYMBICORT (200 mg twice daily (≥111) had a absolute risk decrease of 0.3% at 1 year and 1.5% at 5 years. The 95% confidence interval for the 1-year absolute risk reduction for SYMBICORT was (−0.4% to 0.2%) with a p-value greater than 0.05, indicating no significant difference from placebo. The results from a large population-based prospective cohort epidemiological study reviewing data from the sleep disorders before performing adenotonsillectomy. By including children with OSA, the study will be a comprehensive review and analysis of existing studies on adenotonsillectomy in children with OSA.
Nighttime caffeine delayed circadian clock

BY AMY KARON
Frontline Medical News

A double espresso-sized dose of caffeine consumed 3 hours before bedtime delayed the normal onset of the melatonin rhythm by about 40 minutes, researchers reported in Science Translational Medicine.

"In addition to increasing daytime exposure to sunlight and reducing evening exposure to electrical light, avoiding evening caffeine may help treat problematic delayed sleep timing," according to Tina Burke of the University of Colorado Boulder and her associates.

The results also could support consuming caffeine in the morning to help recover from jet lag, but further studies would need to test that possibility, the researchers added.

Caffeine is known to affect circadian rhythms in rats and flies, but its circadian effects in humans were unknown, the investigators said.

Their 49-day, double-blinded study included five healthy, normal-weight adults who averaged 24 years of age. For a week before each scheduled laboratory visit, participants slept 8 hours a night as verified with the help of sleep logs, wrist actigraphy, and time-stamped voice mail reminders. In the laboratory, they received caffeine or placebo 3 hours before their normal bedtime and were exposed to either bright or dim (control) light at bedtime (Sci Transl Med. 2015;7:1-9).

Bright light with placebo led to about an 85-minute phase delay (P = .0007), while bright light plus caffeine caused a 105-minute shift (P = .0003).

Experiments with cultured human cells also showed that caffeine competitively bound to adenosine receptors, which disrupted signaling of cyclic adenosine monophosphate (cAMP), a key part of the circadian clock, the researchers said.

The study was funded by the National Institutes of Health, the National Center for Advancing Translational Sciences, and the Howard Hughes Medical Institute in collaboration with the University of Colorado.

Ms. Burke reported no relevant financial conflicts.
Alcohol and marijuana use is common in youth with chronic disease, and alcohol use is associated with nonadherence to treatment, according to a new study published in Pediatrics. Approximately one in four American youths are living with a chronic medical condition. The most common substance abused by young people is alcohol, which can lead to adverse medication interactions and difficulty with treatment adherence and self-care. As with healthy youth, alcohol abuse may be associated with poor sleep, smoke exposure, and unprotected or unplanned sex. Marijuana use can lead to airway inflammation, treatment nonadherence, and sleep disturbances. Currently, there are no studies that indicate marijuana has therapeutic utility in young people.

Elissa Weitzman of Harvard Medical School in Boston, and colleagues sought to fill in knowledge gaps on the prevalence of substance use in chronically ill youth. Approximately one in four American youths are living with a chronic medical condition. The most common substance abused by young people is alcohol, which can lead to adverse medication interactions and difficulty with treatment adherence and self-care. As with healthy youth, alcohol abuse may be associated with poor sleep, smoke exposure, and unprotected or unplanned sex. Marijuana use can lead to airway inflammation, treatment nonadherence, and sleep disturbances. Currently, there are no studies that indicate marijuana has therapeutic utility in young people.

Approximately one in four American youths are living with a chronic medical condition. The most common substance abused by young people is alcohol, which can lead to adverse medication interactions and difficulty with treatment adherence and self-care. As with healthy youth, alcohol abuse may be associated with poor sleep, smoke exposure, and unprotected or unplanned sex. Marijuana use can lead to airway inflammation, treatment nonadherence, and sleep disturbances. Currently, there are no studies that indicate marijuana has therapeutic utility in young people.

The investigators conducted a cross-sectional web-based assessment of youth aged 9-18 years who were being treated for cystic fibrosis, asthma, arthritis, type 1 diabetes, or inflammatory bowel disease (IBD). The questionnaire assessed alcohol use, behaviors, marijuana use, and health care interactions (Pediatrics 2015. doi: 10.1542/peds.2015-0722).

Of the 532 youths invited to participate in the study, 403 consented to participate; 51.6% were female, and 75.1% were white. The average age of participants was 15.6 years, and overall they were in good mental health. Alcohol use within the past year was reported in 30.8%, and older age correlated to alcohol use (P less than .001).

Binge drinking was reported in 37.7% of respondents who reported alcohol use within the past year, and 10.4% in the total group. Binge drinking was reported more often in older (P less than .001) and white (P less than .01) chronically ill youth. Better mental health scores were associated with binge drinking (P less than .01).

Marijuana use was reported in 17.2% of the study group and 20.6% of the high school-aged group. Furthermore, marijuana use in chronically ill youth was associated with males, older age, lower socioeconomic status (P less than .01), and poorer mental health (P less than .01). Participants with IBD had higher rates of marijuana use than participants with arthritis or asthma. Almost all youth who reported past-year marijuana use also reported past-year alcohol use, the investigators noted.

Knowledge of alcohol’s potential effects with medications and laboratory results was low, with only 53.1% and 37.2% of high school students answering correctly, respectively. Those who answered incorrectly were 8.33 and 4.46 times more likely to drink and binge drink (P less than .001). Approximately 8.3% and 32% of the high school-aged participants reported skipping or forgetting to take prescription medications within the past 30 days, respectively. Intentional nonadherence was associated with lower mental health scores (P less than .001).

High school-aged youth who admitted to alcohol use within the past year were 1.61 times and 1.79 times more likely to skip and forget their medications, respectively.

Ms. Weitzman and her associates noted that the association of poorer mental health scores with binge drinking may be related to the social aspect, whereas the association of poorer mental health scores with marijuana may be related to its possible use to improve symptoms.

The authors also pointed out that although nonadherence was associated with alcohol use and poorer mental health scores, it also may be related to health-risking behaviors, poor self-regulation, and the feeling of invulnerability associated with adolescent development.

Alcohol and marijuana use are prevalent among youth with chronic medical conditions, and drinking is associated with treatment nonadherence. Education and screening of medically vulnerable youth are warranted to ameliorate risk,” they concluded.

The authors reported no disclosures, and the study was supported by a National Institutes of Health grant.

First-time youth tobacco users turning to e-cigarettes

First-time youth tobacco users are turning to e-cigarettes, a survey showed.

Researchers examining the results of the survey of 2,084 11th- and 12th-grade participants in the Southern California Children’s Health Study during the spring of 2014 found that e-cigarettes were enjoying a “favorable social environment” among this group.

“This finding is a cause for concern because e-cigarettes were the dominant tobacco product used, and a substantial portion of e-cigarette users had no history of tobacco use,” Jessica L. Barrington-Trimis, Ph.D., a researcher at the University of Southern California’s department of preventive medicine, and her colleagues said in the August issue of Pediatrics (doi:10.1542/peds.2015-0639).

Twenty-four percent of teens reported any lifetime e-cigarette use; 10% were current users (past 30 days) and 14% were past users. “Notably, a lower proportion of adolescents (n = 390, 18.2%) had ever smoked a cigarette; 5.7% (n = 119) were current cigarette users and 10.0% (n = 271) were past cigarette smokers,” Dr. Barrington-Trimis and her associates reported.

The investigators suggested that because of a more favorable perception of e-cigarettes (for example, 43% of the adolescents predicted that their friends would react positively to their own e-cigarette use), they “could contribute to the ‘renormalization’ of tobacco products generally,” and called for more research in this area.

Research was funded by a grant from the National Cancer Institute and the Food and Drug Administration Center for Tobacco Products. The authors reported no relevant financial conflicts of interest.

By Shannon Aymes

By Gregory Twachtman

By Shannnon Aymes
Many techniques for repair of aortic dissection have evolved, but no trials have compared those techniques to determine which is the best.

However, a study team has attempted to evaluate a surgical approach (the “David technique”) that includes three specific steps – no aortic cross clamp, the use of deep hypothermic circulatory arrest (DHCA), and the antegrade resumption of cardiopulmonary bypass. They found that this approach yielded significantly better long-term outcomes than did other approaches tried.

The study investigators, led by Dr. Jennifer S. Lawton of Washington University in St. Louis, reported their findings in the Journal of Thoracic and Cardiovascular Surgery (2015 Aug;130(2):294-301.e1). “We hypothesized that a surgical strategy to prevent cross-clamp injury or false lumen pressurization would be associated with reduced morbidity, mortality, persistent false lumen patency, and improved survival,” Dr. Lawton and her coauthors wrote.

“This study was designed to determine the differences in outcomes between operative techniques,” they said.

At 5 years, the predicted survival was 86% for Group 1 (the ‘David technique’) and 56% for Group 2 (a variety of techniques); and at 10 years, 72% and 37%, respectively.

Aortic dissection repair is a critical question, making the comparison and interpretation of this study difficult. “There are more questions to consider from this study than answers derived from the data about the clamp strategy,” he said.

But, Dr. Shemin said, using the cross-clamp with antegrade antegrade perfusion is “not a major issue.” And the use of clamping during the cooling period can save overall cardiac arrest time during the operation. “If one does use femoral cannulation, then not applying the cross-clamp until achieving circulatory arrest is prudent,” he said. “With antegrade cannulation, one achieves antegrade perfusion so early cross-clamping can be safely performed with the advantages of saving operative time.”

The clamp site must be inspected during circulatory arrest. Antegrade cerebral perfusion is proven to be an excellent technique and is facilitated by right axillary cannulation, Dr. Shemin said. “Most importantly, establishing antegrade CPB [cardiopulmonary bypass] perfusion after circulatory arrest is mandatory in all cases to minimize distal aorta trauma,” he said.

Dr. Richard J. Shemin is a cardiothoracic surgeon at UCLA Medical Center, Santa Monica, Calif.

‘David technique’ may enhance aortic repair

**Key clinical point:** An operation to repair Type A aortic dissection that involves three specific steps achieves better outcomes than do other surgical approaches.

**Major finding:** Survival rates at 5 years were 86% for the group that had operations in which the surgeons used the three specific steps vs. 56% for the other group.

**Data source:** Retrospective analysis of single-center population of 146 patients who had repairs for Type A aortic dissection.

**Disclosures:** None of the study coauthors had any relationships to disclose.

The study evaluated 196 patients who had surgery for acute Type A aortic dissection over 17 years. Group 1, comprising 49 patients, had the operation according to the protocol that involved the three specific steps, as Dr. Tironie David of the University of Toronto first reported in 1999 (Ann. Thorac. Surg. 1999;67:1999-2001) — the “David technique,” as the study authors called it.

Group 2 consisted of patients whose repair involved a variety of techniques, including one or two steps of the David technique but not all three.

Study endpoints were 30-day mortality rate, postoperative adverse events, presence of a false aortic lumen, and overall survival, the latter defined as the time from the date of surgery to the date of death or last follow-up.

The evaluation included examination of patients’ latest CT scan or MRI that was at least 6 months after the operation for false lumen, but only 78 patients had imaging at that interval.

Patients in Group 1 had a higher rate of persistent false lumen — 74% vs. 68% in Group 2.

Thirty-day mortality was 6.1% in Group 1 and 15.7% in Group 2, but Dr. Lawton and her coauthors said this difference was not statistically significant.

Survival rates at 1, 5, and 10 years among both groups were “consistent with published ranges,” the authors said.

At 5 years, the predicted survival was 86% for Group 1 and 56% for Group 2; and at 10 years, 72% and 37%, respectively.

The study authors acknowledged the controversy that surrounds the use of retrograde resumption of cardiopulmonary bypass after replacement of the ascending aorta and that there’s no consensus on which method is best for resuming cardiopulmonary bypass after repair of a type A aortic dissection.

The study also found no difference in the incidence of false lumen between the two groups, but again, this is a source of controversy.

“Persistence of a false lumen following repair for type A aortic dissection has been reported to be associated with poor prognosis and reduced long-term survival,” Dr. Lawton and her study colleagues said.

“Others have reported a patent false lumen was not an independent predictor of late reoperation, but was a predictor of aortic growth following repair of type A aortic dissection,” the investigators commented.

The study authors said one limit of their findings is its retrospective nature, but they also said that a prospective, randomized trial would be difficult to conduct.

None of the study coauthors had any relationships to disclose. They presented their original data at the American Association for Thoracic Surgery Aortic Symposium, April 24-25, 2014, in New York.

**Dr. G. Hossein Almassi, FCCP,** comments: The goal of repair of Type A aortic dissection is to repair the ascending aorta expeditiously and to establish antegrade perfusion in the aorta to prevent pressurization of the false channel. This is usually accomplished by establishment of antegrade perfusion through a right axillary artery cannulation for cardiopulmonary bypass, avoidance of aortic cross clamping, and the use of deep hypothermic circulatory arrest, the so-called David technique (not to be confused with David procedure for aortic root repair). The authors of this study reviewed 196 patients with type A aortic dissection at their institution that underwent repair with a variety of techniques over a 17-year period. They found improved 5- and 10-year patient survival with the David technique. There were only 49 patients in the David technique group, indicating a more recent adoption of this technique with more refinements of surgical and perioperative care techniques. The comments of Dr. Shemin on clamping the ascending aorta during the cooling period to reach the desirable temperature for the establishment of DHCA – and, thus, shortening the operative time in these emergent operations – are germane.

With application of a well-defined institutional protocol for repair of this devastating aortic pathology, good surgical outcomes with acceptably low mortality rates are to be expected.
VIBATIV is the only once-daily bactericidal antibiotic with a dual mechanism of action indicated for infections due to MRSA.

Take the next step with VIBATIV—the re-engineered vancomycin molecule—when serious MRSA infections call for P.L.U.S.:

**P**otent *in vitro* bactericidal action against Gram-positive pathogens

**L**evels of drug that remain above the MIC\(_{90}\) for MRSA over 24 hours

**U**ser-friendly, once-daily dosing without therapeutic drug-level monitoring

**S**afety profile characterized in large clinical trials
VIBATIV is the only once-daily bactericidal antibiotic indicated for the treatment of HABP/VABP due to MRSA

INDICATION
VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *VIBATIV* should be reserved for use when alternative treatments are not suitable.

VIBATIV is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive microorganisms:

- *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)
- *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or
- *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to telavancin. VIBATIV should be initiated as empiric therapy before results of these tests are known. To reduce the development of drug-resistant bacteria and maintain the effectiveness of VIBATIV and other antibacterial drugs, VIBATIV should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Available in two strengths: 250 mg and 750 mg

**IMPORTANT SAFETY INFORMATION**

**Mortality**
Patients with pre-existing moderate/severe renal impairment (CrCl $\leq$ 50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl $\leq$ 50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

**Nephrotoxicity**
New onset or worsening renal impairment occurred in patients who received VIBATIV. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction and in patients who received concomitant medications known to affect kidney function.

Monitor renal function in all patients receiving VIBATIV prior to initiation of treatment, during treatment, and at the end of therapy. If renal function decreases, the benefit of continuing VIBATIV versus discontinuing and initiating therapy with an alternative agent should be assessed.

**Fetal Risk**
Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. Avoid use of VIBATIV during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. If not already pregnant, women of childbearing potential should use effective contraception during VIBATIV treatment.

**Contraindication**
VIBATIV is contraindicated in patients with a known hypersensitivity to the drug.

**Hypersensitivity Reactions**
Serious and potentially fatal hypersensitivity reactions, including anaphylactic reactions, may occur after first or subsequent doses. VIBATIV should be used with caution in patients with known hypersensitivity to vancomycin.

**Geriatric Use**
Telavancin is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group.

**Infusion Related Reactions**
VIBATIV is a lipoglycopeptide antibacterial agent and should be administered over a period of 60 minutes to reduce the risk of infusion-related reactions. Rapid intravenous infusions of the glycopeptide class of antimicrobial agents can cause “Red-Man Syndrome”-like reactions including: flushing of the upper body, urticaria, pruritus, or rash.

**QTc Prolongation**
Caution is warranted when prescribing VIBATIV to patients taking drugs known to prolong the QT interval. In a study involving healthy volunteers, VIBATIV prolonged the QTc interval. Use of VIBATIV should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy.

**Most Common Adverse Reactions**
The most common adverse reactions (greater than or equal to 10% of patients treated with VIBATIV) were taste disturbance, nausea, vomiting, and foamy urine.

VBT 00046-04
August 2014
surgery. When performing on-pump coronary artery bypass grafting (CABG), cardiac surgeons can control very few factors to reduce the risk of stroke – with the exception of which method of aortic manipulation they use. Debate and controversy, however, have surrounded which aortic manipulation technique is best: single- or double-clamp occlusion. A large retrospective study of almost 8,500 patients who had CABG at the Mayo Clinic in Rochester, Minn., over a 17-year period showed that, while use of the single-aortic cross-clamp (SC) technique steadily increased, the risk of stroke is virtually the same as it is with the partial aortic cross-clamp (PC), or double-cross-clamp, technique. The study authors, led by Dr. Juan C. Araque, published their results online in the Journal of Thoracic and Cardiovascular Surgery (2015. doi: 10.1016/j.jtcvs.2015.04.010).

“It is intuitive that less aortic manipulation would result in less risk of stroke,” Dr. Araque and colleagues write, but even off-pump CABG, which requires no aortic manipulation, is not without stroke risk.

“It is conceivable that there is Continued on following page
NEW YORK – Displaying a low-tech, low-cost white board in the operating room during the “time out” before surgery can significantly improve memory retention among members of the surgical team, a new study suggests.

“We found that providing a white board that you can buy at any office supply store gives a visual stimulus on top of the verbal stimulus that improves retention of important information,” Dr. Aryan Meknat, the study author, said at the annual Minimally Invasive Surgery Week.

A surgical pause or “time out” performed before any operative procedure is a major component of the Joint Commission’s Universal Protocol to prevent wrong site, wrong procedure, and wrong person surgery.

Retention of information presented during the surgical pause is essential, at the beginning of the case and for the duration of the procedure, he said.

During the study, surgical teams were randomly divided into two groups: In the first group, 30 team members were given information verbally during the surgical pause; while a second group of 29 team members was provided with verbal information that was read from the white board. The white board was displayed in the operating room throughout the surgical procedure for the second group.

After the conclusion of the procedure, the white board was removed and both groups were given a short written questionnaire.

Each team was tested only once in order to keep the study blinded. Also, participants had no prior knowledge that they would be tested after the procedure.

Study participants were asked to recall several facts about the patient, including the patient’s first and last name, age, sex, weight, site of IV placement, allergies, medications, relation of accompanying guardian, and the signature on the consent form.

Team members in the first study group answered a total of 300 questions, and 200 questions (66.7%) were correctly answered. Participants in the second group—which used the white board—answered 290 questions, and 239 (82.4%) were correctly answered. The white board group had a 23.6% overall increase in correctly answered questions.

The difference between retention in the two groups was statistically significant (P < .05) in every category tested.

“These findings apply to operating rooms everywhere, especially in cases where there may be long delays before starting the procedure, changes in anesthesiology midcase, situations where two procedures are scheduled in one patient, or in intraoperative emergency situations. ‘We need to be sure that the surgical team retains information, as well as [listens] to verbal instructions,’ said Dr. Meknat of MobiSurg, a mobile surgical unit based in Laguna Hills, Calif.

Dr. Meknat reported having no relevant financial disclosures.
The term ‘intestinal microbiome’ vaguely refers to the ecological community of commensal, symbiotic, and potentially pathogenic microbes living within the human alimentary tract. These organisms play various key roles in energy uptake, vitamin synthesis, epithelial homeostasis, and immunity development. In recent years, there has been an ever-increasing interest in the intestinal microbiome and its potential implications for critically ill patients. A simple PubMed.gov search shows a more than 25-fold increase in the number of publications on this topic over the past decade, from 63 papers in 2004 to 1,716 articles in 2014.

While accumulating data suggest that the density and diversity of the bowel flora are of central importance in maintaining homeostasis, our understanding of host-microbe interactions is in its relative infancy. We know that the gut microbiota typically contains hundreds of trillions of microorganisms, including over 1,000 different species and more than 3 million genes. It is estimated that about a third of the microbiota is common to all humans but that the remaining two-thirds is specific to each person as his/her fingerprints. However, unlike our fingerprints, the gut flora is a malleable entity affected by diet, medications, acute illness, and a host of other factors.

The potential clinical utility of alterations in the intestinal microbiome is not an entirely novel frontier for intensivists. Rather, there have long been various levels of speculation and/or evidence regarding the role of the GI microbes in the pathogenesis of such diverse ICU entities as antibiotic-associated diarrhea, sepsis, ventilator-associated pneumonia, and Clostridium difficile diarrhea. Conflict arises because in some scenarios, obliteration of the normal gut microbiome (e.g., the C. difficile diarrhea being the classic example) is beneficial, while in other instances, the same flora are implicated as the culprit (sepsis and ventilator-associated pneumonia).

This juxtaposition of yin and yang lies at the heart of one unique dilemma in managing critically ill patients: Are the intestinal microbiota friends or foes? Should we be sterilizing the gut or constantly replenishing this ecosystem? Selective oral decontamination (SOD) and selective digestive decontamination (SDD) are strategies that view the gut microbiome as enemies and are used to prevent ventilator-associated pneumonia. SOD attempts to sterilize the upper aerodigestive tract through the use of topical broad-spectrum antibiotics while SDD extends the zone of combat to include the entire alimentary tract by adding several doses of systemic antibiotics to the topical oral agents. Presumably through the reduction of the density of the gut flora, these strategies have repeatedly been shown to be effective in preventing pneumonia. More importantly, this remarkably low-cost strategy significantly reduces mortality, as well. It should be noted that SOD and SDD are not currently endorsed by existing pneumonia guidelines in the United States, given significant concerns for potential adverse effects of widespread use on local antibiotics if incorporated into routine practice.

A diametrically opposite strategy—one that views the flora as the solution and not the problem—is the concept of probiotic administration. Probiotics are microorganisms of human origin that survive when ingested, colonize the intestines, and subsequently confer health benefits upon the host. Related concepts include prebiotics (undigestible products that promote growth of beneficial microbes) and symbiotics (combinations of probiotic and prebiotic agents). Probiotic species have a variety of theoretic mechanisms whereby they may have effects on the host including probiotics’ direct competition with pathogens, release of factors to create a locally hostile environment for pathogens, and immunomodulation. Of these, immunomodulation appears to be of increasing importance and significance. Briefly, immunomodulation involves complex interactions between probiotic species and intestinal dendritic cells to polarize T cells, a sequence of events that ultimately optimizes mucosal integrity, as well as local and systemic immunity.

To date, existing studies viewing the microbiota as a friendly entity—the probiotic approach—are relatively few in number and have limitations due to sample size and/or methodologic issues. Current systematic reviews and meta-analyses have concluded that probiotics generally appear to confer benefits for selected indications but that extensive further study is needed before definitive conclusions can be made. The probiotic strategy also has the added potential safety concern inherent to treating critically ill patients with living microbes. Critics of the probiotic strategy point to the PROPATRIA trial, a randomized, controlled study in patients with predicted severe pancreatitis that showed increased mortality in probiotic-treated patients. While this study appears to be an outlier and the increased mortality may have been due to study-specific issues, this finding reiterates the need for meticulous attention to safety when prescribing probiotics.

So, we return to the fundamental question: is the intestinal microbiome our friend or is it our foe? Not surprisingly, the answer appears to be both. Given the immense diversity of the normal adult gut flora, we should expect both beneficial and harmful effects ultimately depending on the relative balance of the microbiome’s beneficial and potentially harmful constituents. Maintaining this balance, then, becomes an important therapeutic target. However, the aforementioned microbial variability between individuals and the propensity for the flora to change over time within an individual presents challenges when attempting to therapeutically alter the microbiome and improve outcomes. Moreover, might there be select populations that might disproportionately benefit from manipulations of the gut flora? Thinking outside the box, maybe the microbiota dysbiosis seen with obesity confers protection—the so-called obesity paradox.

While accumulating data suggest that the density and diversity of the bowel flora are of central importance in maintaining homeostasis, our understanding of host-microbe interactions is in its relative infancy. Of the normal adult gut flora, we should expect both beneficial and harmful effects ultimately depending on the relative balance of the microbiome’s beneficial and potentially harmful constituents. We might therefore be sterilizing the gut or constantly replenishing this ecosystem? Selective oral decontamination (SOD) and selective digestive decontamination (SDD) are strategies that view the gut microbiome as enemies and are used to prevent ventilator-associated pneumonia. SOD attempts to sterilize the upper aerodigestive tract through the use of topical broad-spectrum antibiotics while SDD extends the zone of combat to include the entire alimentary tract by adding several doses of systemic antibiotics to the topical oral agents. Presumably through the reduction of the density of the gut flora, these strategies have repeatedly been shown to be effective in preventing pneumonia. More importantly, this remarkably low-cost strategy significantly reduces mortality, as well. It should be noted that SOD and SDD are not currently endorsed by existing pneumonia guidelines in the United States, given significant concerns for potential adverse effects of widespread use on local antibiotics if incorporated into routine practice.

A diametrically opposite strategy—one that views the flora as the solution and not the problem—is the concept of probiotic administration. Probiotics are microorganisms of human origin that survive when ingested, colonize the intestines, and subsequently confer health benefits upon the host. Related concepts include prebiotics (undigestible products that promote growth of beneficial microbes) and symbiotics (combinations of probiotic and prebiotic agents). Probiotic species have a variety of theoretic mechanisms whereby they may have effects on the host including probiotics’ direct competition with pathogens, release of factors to create a locally hostile environment for pathogens, and immunomodulation. Of these, immunomodulation appears to be of increasing importance and significance. Briefly, immunomodulation involves complex interactions between probiotic species and intestinal dendritic cells to polarize T cells, a sequence of events that ultimately optimizes mucosal integrity, as well as local and systemic immunity.

To date, existing studies viewing the microbiota as a friendly entity—the probiotic approach—are relatively few in number and have limitations due to sample size and/or methodologic issues. Current systematic reviews and meta-analyses have concluded that probiotics generally appear to confer benefits for selected indications but that extensive further study is needed before definitive conclusions can be made. The probiotic strategy also has the added potential safety concern inherent to treating critically ill patients with living microbes. Critics of the probiotic strategy point to the PROPATRIA trial, a randomized, controlled study in patients with predicted severe pancreatitis that showed increased mortality in probiotic-treated patients. While this study appears to be an outlier and the increased mortality may have been due to study-specific issues, this finding reiterates the need for meticulous attention to safety when prescribing probiotics.

So, we return to the fundamental question: is the intestinal microbiome our friend or is it our foe? Not surprisingly, the answer appears to be both. Given the immense diversity of the normal adult gut flora, we should expect both beneficial and harmful effects ultimately depending on the relative balance of the microbiome’s beneficial and potentially harmful constituents. Maintaining this balance, then, becomes an important therapeutic target. However, the aforementioned microbial variability between individuals and the propensity for the flora to change over time within an individual presents challenges when attempting to therapeutically alter the microbiome and improve outcomes. Moreover, might there be select populations that might disproportionately benefit from manipulations of the gut flora? Thinking outside the box, maybe the microbiota dysbiosis seen with obesity confers protection—the so-called obesity paradox.

At present, there are no widely available commercial tests to assess the given patient’s microbiome—and there are no well-defined ‘targets’ for manipulation. In our critically ill patients, the flora’s eternal evolution rapidly accelerates with abrupt changes brought on by dietary changes, various medications, and acute illness itself, turning our ill-defined target into a moving ill-defined target. Adding further insult to injury, there is a host of unknowns when we consider probiotic therapy as a means to rebalance the intestinal microbiota. What are the optimal probiotic species to use? What are the threshold densities that must be achieved to effect change? Is colonization important or is ingestion of nonviable organisms equally effective? What are the optimal routes of probiotic administration? What are the implications of ICU nutrition and/or medications?

Perhaps in the end, these fundamental questions are more important than determining ‘friends’ and ‘foes.’ Ideally, evidence-based nutritional guidelines (including the anticipated upcoming revisions to the ASPEN nutrition guidelines) will continue to highlight the potential for, as well as the knowledge gaps, surrounding microbiome manipulation therapy. Ideally, such attention to this expensive and widely available therapeutic option will pressure funding sources and regulatory agencies to further exploration of these issues and to help ICU care evolve in this novel direction.

Dr. Morrow is Section Editor for Critical Care Commentary.

References
Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta₂-adrenergic agonist 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.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Once-daily ANORO ELLIPTA significantly improved lung function by 167 mL (P<0.001) vs placebo at Day 169*

*As measured by the primary endpoint, trough (predose) FEV₁ at Day 169 (mean of the FEV₁ values at 23 and 24 hours after dosing on Day 168), in a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Least squares mean change from baseline of 171 mL for ANORO ELLIPTA (n=413) and 4 mL for placebo (n=280).

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

- Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.
- The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

CONTRAINDICATIONS

- The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients.

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.

Please see additional Important Safety Information for ANORO ELLIPTA on the following pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for ANORO ELLIPTA following this advertisement.
Lung function comparison studies with tiotropium

Indications
- ANORO ELLIPTA is a combination anticholinergic/LABA indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD.
- SPIRIVA HandiHaler® (tiotropium bromide inhalation powder) is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.2

Description of Studies3-5

Design: Three 24-week, multicenter, randomized, blinded, active-controlled, double-dummy, parallel-group studies that evaluated the efficacy and safety of ANORO ELLIPTA (administered once daily by the ELLIPTA inhaler) and other treatment arms, including tiotropium 18 mcg (administered once daily by the HandiHaler).

Treatment arms: In the 1st study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or VI 25 mcg.1 In the 2nd study, patients were randomized to treatment with ANORO ELLIPTA, tiotropium 18 mcg, UMEC/VI 125 mcg/25 mcg,* or UMEC 125 mcg.* In the 3rd study, patients were randomized to treatment with ANORO ELLIPTA or tiotropium 18 mcg.

Patients: Studied in patients (mean age range: 62 to 65 years) with COPD. At screening, patients had a mean postbronchodilator FEV1 range of 46.4% to 47.7% predicted, a mean reversibility range of 11.7% to 15.6%, and a mean postbronchodilator FEV1/FVC ratio range of 0.46 to 0.48.

Primary endpoint: Trough (predose) FEV1 at Day 169 (defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168).

FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; UMEC=umeclidinium; VI=vilanterol.
*UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg are not approved strengths.
1Vilanterol is not approved as monotherapy.
SPIRIVA and HandiHaler are registered trademarks owned by Boehringer Ingelheim.

Important Safety Information for ANORO ELLIPTA (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA 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 cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.
- Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician 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 physician immediately if signs or symptoms of urinary retention develop.
- Be alert to hypokalemia and hyperglycemia.

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

**PRIMARY ENDPOINT:** TROUGH (PREDOSE) FEV1, AT DAY 1691,4

<table>
<thead>
<tr>
<th>Study</th>
<th>ANORO ELLIPTA (n=207)</th>
<th>Tiotropium 18 mcg (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Study–DB2113360</td>
<td>211 mL</td>
<td>121 mL</td>
</tr>
<tr>
<td>2nd Study–DB2113374</td>
<td>208 mL</td>
<td>149 mL</td>
</tr>
<tr>
<td>3rd Study–ZEP117115</td>
<td>205 mL</td>
<td>93 mL</td>
</tr>
</tbody>
</table>

The comparison of UMEC/VI 125 mcg/25 mcg with UMEC 125 mcg preceded that of ANORO ELLIPTA with tiotropium as part of a predefined hierarchy of treatment differences and did not achieve statistical significance. Therefore, results of the comparison of ANORO ELLIPTA with tiotropium were descriptive only and statistical significance could not be inferred.3

3Reflects rounding.

LS=least squares.

---

**Adverse events (AEs) occurring in ≥3% of subjects in any of the 3 studies2–5**

Safety data were descriptive only. The studies were not powered to compare the safety profile of ANORO ELLIPTA with that of tiotropium. The range of AEs across the 3 studies for ANORO ELLIPTA (n=883) and tiotropium 18 mcg (n=874), respectively, were:

- Headache: 9–10% vs. 4–7%
- Nasopharyngitis: 6–10% vs. 7–8%
- Back pain: 2–5% vs. 2–5%
- Lower respiratory tract infection: 0–4% vs. <1–1%
- Upper respiratory tract infection: <1–4% vs. <1–7%
- COPD: <1–3% vs. <1–2%
- Cough: 2–3% vs. 2–3%
- Gastritis: 0–3% vs. <1%
- Pain in extremity: <1–3% vs. <1–2%
- Hypertension: <1–2% vs. <1–3%
- Urinary tract infection: 0–<1% vs. <1–3%

**Important Safety Information for ANORO ELLIPTA (cont’d)**

**DRUG INTERACTIONS**

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, neflinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA 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, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they 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 electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

**References:**


Please see additional Important Safety Information for ANORO ELLIPTA on preceding pages.

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

**www.GSKSource.com**

©2015 GSK group of companies. All rights reserved. Printed in USA. 18341180 April 2015

ANORO ELLIPTA was developed in collaboration with Theravance
5.7 Cardiovascular Effects

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions, with signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

5.10 Worsening of Urinary Retention

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

5.11 Hypokalemia and Hyperglycemia

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

6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related deaths. ANORO ELLIPTA is not indicated for the treatment of asthma. [See Based Warning and Precautions (5.5)].

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

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

6.1 Clinical Trials Experience

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

The clinical program for ANORO ELLIPTA included 8,118 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

6-Month Trials: The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 66% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV1) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV1, forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, active control, or placebo.

Table 1. Adverse Reactions With ANORO ELLIPTA With <1% Incidence and More Common Than With Placebo In Patients With Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n = 550)</th>
<th>ANORO ELLIPTA (n = 842)</th>
<th>Umeclidinium 62.5 mcg (n = 841)</th>
<th>Vilanterol 25 mcg (n = 834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>&lt;1%</td>
<td>1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Neck pain</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

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

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

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when...
Vilanterol should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of non-potassium-sparing diuretics. In these cases, use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce cardiovascular toxicity and metacarpals.

Nonteratogenic Effects: Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 58 and 200 times, respectively, the MRHDID in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal inhaled doses up to 33,760 mcg/m²/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/m²/kg/day in rabbits). Fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Umeclidinium: There was no evidence of teratogenic effects in rats and rabbits at approximately 58 and 200 times, respectively the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults on a mcg/m² basis (at maternal inhaled doses up to 33,760 mcg/m²/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/m²/kg/day in rabbits). Fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

Nonteratogenic Effects: Umeclidinium: There were no effects on perinatal and postnatal developments in rats at approximately 60 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day). Vilanterol: There were no effects on perinatal and postnatal developments in rats at approximately 3,800 times the MRHDID in adults (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/m²/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery. Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

ANORO ELLIPTA: It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman.

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovular tubulostomal adenomas in females at an inhalation dose of 25.5 mg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis). In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas and fibroids in females and shortening of the latency of pulmonary tumors at inhalation doses greater than or equal to 84.4 mg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis). These tumor findings in rodents are similar to those reported previously for other beta-agonist agonist drugs. The relevance of these findings to human use is unknown.

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

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31.5,000 mg/kg/day (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m² basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). Asthma-Related Death: Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-death death. ANORO ELLIPTA is not indicated for the treatment of asthma.

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol.

Provide patients with such medicine and instruct them in how it should be used. Inform patients to seek medical attention immediately if they experience any of the following:

• Symptoms get worse
• Need for more inhalations than usual of their rescue inhaler

Instruct patients who have been taking inhaled, short-acting beta2-agonists on a regular basis to discontinue the use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm.

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

Not for Acute Symptoms: Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol.

Provide patients with such medicine and instruct them in how it should be used. Inform patients to seek medical attention immediately if they experience any of the following:

• Symptoms get worse
• Need for more inhalations than usual of their rescue inhaler

Instruct patients who have been taking inhaled, short-acting beta2-agonists on a regular basis to discontinue the use of these products and use them only for the symptomatic relief of acute symptoms.

Paradoxical Bronchospasm: As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm.

Inform patients of adverse effects associated with beta 2-agonists, including cardiac effects (e.g., angina, hypertension, tachycardia, with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility ANORO ELLIPTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umclidinium and vilanterol, as described below.

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

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

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

Vilanterol: In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovular tubulostomal adenomas in females at an inhalation dose of 25.5 mg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis). In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas and fibroids in females and shortening of the latency of pulmonary tumors at inhalation doses greater than or equal to 84.4 mg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

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

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

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31.5 mg/kg/day and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m² basis).
Scoring tool may reveal ventilator dependence risk

BY PATRICE WENDLING
Frontline Medical News

CHICAGO – A new preoperative risk scoring tool may help identify patients at high risk for requiring mechanical ventilation for more than 48 hours in the 30 days after surgery, a study suggests. The risk score is based on seven measures: whether patients have had a small bowel procedure, have had an esophageal procedure, are current smokers, have severe chronic obstructive pulmonary disease, have hypoalbuminemia, are older than age 60 years, or have signs of systemic inflammatory response syndrome or sepsis.

The score was validated via the American College of Surgeons (ACS)/National Surgical Quality Improvement Program (NSQIP) database to identify patients who underwent nonemergent general or vascular surgery at Thomas Jefferson University Hospital between 2006 and 2013. Dr. Adam P. Johnson, study coauthor, reported at the ACS/NSQIP National Conference.

The risk score assigned 1 point each for a small bowel procedure, current smoking, severe chronic obstructive pulmonary disease, and hypoalbuminemia (less than 3.5 mg/dL); 2 points each for age over 60 years and signs of systemic inflammatory response syndrome or sepsis; and 3 points for esophageal procedures. Total risk scores ranged from 0 to 7 points for the population.

The median score was 2 for patients who did not need a ventilator after surgery and 3 for those who did. Notably, patients with a risk score of more than 3 comprised the 20%-30% of patients who experienced 60%-70% of adverse events. A cutoff value of 3 identified the top 20% of patients at highest risk for ventilator dependence, with a ventilator dependence rate of 5.4% (P less than .01). The risk factors and scoring system are specific to Thomas Jefferson University Hospital. However, other institutions should be able to use the methodology and framework to identify ventilator risk factors in their own patients, Dr. Johnson suggested.

Future steps include evaluating how the risk tool performs when compared with risk scores derived from national datasets, automating the best performing risk score, and using the score in the preadmission testing of every patient undergoing elective general surgery or vascular operations. Once identified, high-risk patients would then be entered into an aggressive pre-, intra-, and postoperative pulmonary optimization pathway.

"The pathway might be resource intensive for all patients, but we might be able to hone in and use it more effectively for patients at greatest risk," Dr. Johnson said in a statement.

Although ventilator dependence occurs in only about 1%-3% of patients, the consequences are nonetheless significant, increasing mortality and health care costs, said Dr. Scott W. Cowan, senior study author and Jefferson’s NSQIP Surgeon Champion.

pwending@frontlinemedcom.com

Resuscitation type had no laparotomy impact

BY SHARON WORCESTER
Frontline Medical News

LAS VEGAS – Choice of damage control resuscitation versus emergent laparotomy to manage traumatic injury did not affect whether severely injured patients required an emergency laparotomy, or survival following laparotomy.

Major finding: 52% of patients in the 1:1:1-ratio emergency resuscitation group and 50% in the 1:1:2-ratio group underwent emergency laparotomy, and 30-day survival was 82% and 77%, respectively.

Data source: An analysis of data for 680 patients from the PROPPR trial.

Disclosures: Dr. Perl reported having no relevant disclosures.

Of 680 patients who had severe injuries and were predicted to require massive transfusions, 613 underwent a surgical procedure and 397 underwent a laparotomy. Of the latter, 346 were emergency laparotomies. Of those who received damage control resuscitation using the 1:1:1 ratio, 52% underwent emergency laparotomy (defined as laparotomy within 90 minutes of arrival at a trauma center). Of those who received the 1:1:2 ratio, 50% underwent emergency laparotomy. The difference between the groups was not statistically significant, Dr. Perl reported at the annual meeting of the American Association for the Surgery of Trauma.

"We were unable to detect significant effects of damage control resuscitation on the frequency and time to emergency laparotomy [or] outcomes."

The median time to laparotomy was 28 minutes in both groups, and the proportions of patients who survived to 3 hours, 6 hours, 24 hours, and 30 days also were similar in the two groups. For example, 88% and 85% of those in the 1:1:1 and 1:1:2 groups, respectively, survived to 24 hours; 82% and 77%, respectively, survived to 30 days, he said.

There was no overall difference in mortality between the groups (hazard ratio, 0.78), nor was there a difference in survival by study site, he noted.

sworcester@frontlinemedcom.com

Dr. Jennifer Cox, FCCP, comments:
Ventilator dependence after surgery is generally low, but the contributions to health care resource utilization are great. This scoring system is easy to use and predicted which patients have 60%-70% of the adverse events after surgery and the top 20% of patients who had the highest risk for ventilator dependence. The scoring system does not require additional testing above what is traditionally done for preoperative evaluation, which makes it desirable. Of note, two of the criteria were directed at gastrointestinal procedures in an institution where a high volume of GI procedures occurred. The score was calculated on elective and nonemergent general and vascular surgery patients. In my opinion, the utility of this scoring system is not to discourage surgery in high-risk patients, but to quickly identify the high-risk patient for ventilator dependence preoperatively. These high-risk patients can then be triaged into a more-aggressive preoperative, intraoperative, and postoperative pulmonary education program that is patient specific and largely patient centered. This not only allows physician awareness and vigilance, but also puts patients in the driver’s seat to take control and actively participate in their comprehensive care plan for a good outcome.

Frontline Medical News

VITALS

Key clinical point: Choice of damage control resuscitation – plasma:platelet:red blood cell ratio of either 1:1:1 or 1:1:2 – does not affect whether severely injured patients require an emergency laparotomy, time to laparotomy, or survival following laparotomy.

Data source: An analysis of data for 680 patients from the PROPPR trial.

Disclosures: Dr. Perl reported having no relevant disclosures.

VITALS

Key clinical point: Choice of damage control resuscitation – plasma:platelet:red blood cell ratio of either 1:1:1 or 1:1:2 – does not affect whether severely injured patients require an emergency laparotomy, time to laparotomy, or survival following laparotomy.

Major finding: 52% of patients in the 1:1:1-ratio emergency resuscitation group and 50% in the 1:1:2-ratio group underwent emergency laparotomy, and 30-day survival was 82% and 77%, respectively.

Data source: An analysis of data for 680 patients from the PROPPR trial.

Disclosures: Dr. Perl reported having no relevant disclosures.

Of 680 patients who had severe injuries and were predicted to require massive transfusions, 613 underwent a surgical procedure and 397 underwent a laparotomy. Of the latter, 346 were emergency laparotomies. Of those who received damage control resuscitation using the 1:1:1 ratio, 52% underwent emergency laparotomy (defined as laparotomy within 90 minutes of arrival at a trauma center). Of those who received the 1:1:2 ratio, 50% underwent emergency laparotomy. The difference between the groups was not statistically significant, Dr. Perl reported at the annual meeting of the American Association for the Surgery of Trauma.

The median time to laparotomy was 28 minutes in both groups, and the proportions of patients who survived to 3 hours, 6 hours, 24 hours, and 30 days also were similar in the two groups. For example, 88% and 85% of those in the 1:1:1 and 1:1:2 groups, respectively, survived to 24 hours; 82% and 77%, respectively, survived to 30 days, he said.

There was no overall difference in mortality between the groups (hazard ratio, 0.78), nor was there a difference in survival by study site, he noted.

sworcester@frontlinemedcom.com
Lung adenocarcinomas you don’t want to miss

BY SUSAN LONDON
Frontline Medical News

SEATTLE – Many advanced non–small cell lung cancer adenocarcinomas can now be managed with therapies that target driving mutations, but these mutations must be identified and tracked as they can change over time, Dr. Mark A. Socinski said at a joint meeting by Global Biomarkers Consortium and World Cutaneous Malignancies Congress.

The 2013 College of American Pathology guideline for the molecular testing of lung cancer “was a monumental publication and a beachhead, if you will, for establishing a standard of care [for NSCLC], much like we have in breast cancer for ER, PR, and HER2 measurement,” he said. Furthermore, “we are now in an era where doing subsequent or sequential biopsies with repeat molecular testing is a standard of care in this population.”

Although lung adenocarcinomas are homogeneous histologically, they are diverse with respect to oncogenic drivers (JAMA. 2014;311[19]:1998-2006), noted Dr. Socinski, director of the lung cancer section at the University of Pittsburgh Medical Center; clinical associate director of the University of Pittsburgh Lung Cancer SPORE; codirector of the UPMC Lung Cancer Center of Excellence; and coleader of the lung cancer program at the University of Pittsburgh.

“Our major nemesis is KRAS. We still don’t have a good answer for that,” he said. But roughly a third of lung adenocarcinomas have actionable mutations in the genes for EGFR (epidermal growth factor receptor), ALK, ROS1, BRAF, MET, or RET.

“In the year 2015, these are what I look for in our patient population. … We test routinely to identify these populations,” he said. “In my clinic this week, I might have had almost all of these patients on targeted TKIs [tyrosine kinase inhibitors] with these sorts of things, getting clinical benefit in this particular setting.”

Common mutations

“The EGFR mutation story really transformed lung cancer,” Dr. Socinski said. In patients whose adenocarcinomas harbor these mutations, targeted therapy with an EGFR inhibitor commonly nets a dramatic response. “If you see this a number of times and you’re a lung cancer doc, you become addicted to oncotype testing. And you certainly don’t want to ever miss this,” he said.

The IPASS trial (First-Line Iressa Versus Carboplatin/Paclitaxel in Asia) comparing the targeted agent gefitinib (Iressa) with chemotherapy in advanced NSCLC adenocarcinoma among never or light smokers was “a transformational trial in lung cancer,” according to Dr. Socinski (N Engl J Med. 2009;361[10]:947-57).

“The lesson from IPASS: Phenotype we threw out the door; it’s really about genotype. And if you didn’t have the genotype [EGFR mutation], a TKI was very poor treatment. And if you had the genotype, the TKI was superior to chemotherapy,” with a 52% reduction in the risk of progression or death.

Trials testing the EGFR inhibitors erlotinib (Tarceva) and afatinib (Gilotrif) have likewise shown a progression-free survival benefit in this patient population.

“One of the issues that we struggled with for some time was whether there is any survival benefit,” Dr. Socinski said. A recent combined analysis of two afatinib trials has answered that question affirmatively (Lancet Oncol. 2015;16[2]:141-51), and these agents have therefore become standard of care for EGFR-mutant adenocarcinoma.

“Interestingly, as we say, all EGFR mutants are not created equal, because in the exon 21–mutated tumors, actually there was no difference relative to chemotherapy, and that survival advantage is really driven by exon 19. So the nature of your mutation is important in this particular analysis,” he cautioned.

When patients on EGFR targeted therapy develop resistance, the cause in about half of cases is emergence of a secondary mutation in exon 20, the T790M mutation (Sci Transl Med. 2011;3[75]:75ra26).

“The standard of care is to biopsy at the time of progression,” Dr. Socinski maintained. “The reason why rebiopsy is important and it’s important to diagnose that [new mutation] is that we have a couple of drugs close to [FDA approval].”
Irrelevant portions have been removed. The full text is as follows:

The T790M mutation can appear at different times, he said. "I've even got several patients whom we've rebiopsied three or four times, and there has been T790M negativity and then emergence of positivity on subsequent biopsy. Given the activity of these drugs, that's important to know."

Another fairly common actionable mutation in lung adenocarcinoma is ALK, for which oncologists now have crizotinib (Xalkori). Crizotinib has likewise been tested against combination chemotherapy in a phase III trial in which it yielded superior progression-free survival in patients with advanced nonsquamous NSCLC harboring ALK mutations (ASCO 2014. Abstract 8002).

"This is now a second example with a molecular biomarker in which we've replaced the standard of care chemotherapy with a molecularly targeted agent," Dr. Socinski noted. Second-generation ALK inhibitors such as the investigational agent alectinib are showing promise (ASCO 2015. Abstract 8008). "Even in previously crizotinib-exposed patients, these have a great deal of activity and allow another option for sequential therapy in this population of patients," he said.

Uncommon mutations

Driving mutations of ROS1 are found in about 1%-2% of lung cancers, most often in younger never smokers with adenocarcinomas, according to Dr. Socinski. These tumors respond to crizotinib, which is also a ROS1 inhibitor. "In fact I think it may actually be a better ROS1 drug than an ALK drug," he said.

The drug yields an impressive median progression-free survival of 19.2 months and overall response rate of 72% in this setting (N Engl J Med. 2014;371[21]:1963-71), "so ROS1 is another biomarker that we go hunting for in this population, even though you won't see it very commonly."

Mutations of BRAF are found in about 2% of metastatic adenocarcinomas (Cancer. 2015;121[3]:448-456). The large majority, about four-fifths, are of the V600E type. The BRAF inhibitor dabrafenib (Tafinlar) has been associated with an overall response rate of 32% in patients with this specific mutation (abstract LBA38, Ann Oncol. 2014;25[Suppl 4]. doi: 10.1093/annonc/mdu438.46). And preliminary data suggest efficacy increases when it is combined with the Mek inhibitor trametinib (Mekinist) (ASCO 2015. Abstract 8006), as has been seen in melanoma.

About 4% of lung cancers have an intermediate or high level of MET amplification. In a small sample of patients with these tumors, treatment with crizotinib appeared to be active (ASCO 2014. Abstract 8001). In addition, this agent has efficacy against lung cancers having exon 14 splice mutations in MET (ASCO 2015. Abstract 8021). "So this is another genotype not to miss," Dr. Socinski said.

Finally, mutation of RET is seen about 1%-2% of unselected NSCLCs, also typically in young never smokers or former smokers with adenocarcinoma. Cabozantinib (Cometriq), a multitargeted TKI having activity against RET, yields a 28% response rate in RET-rearranged adenocarcinomas (ASCO 2015. Abstract 8007).

A controversial topic for these uncommon mutations in lung adenocarcinomas is how much evidence should be required for new targeted agents to gain FDA approval, Dr. Socinski said. "For instance, the ROS1 experience: Do we really need a randomized trial in a rare genotype to approve this drug [crizotinib] for ROS1-positive patients? I would say, absolutely not," he concluded.

Dr. Socinski disclosed that he receives fees from Celgene and Genentech, and performs contracted research for Celgene, Clovis, Genentech, GlaxoSmithKline, Pfizer, and Synta.
DENVER – The term “precision medicine” can be applied to both clinical care and to pathology, as newly updated staging and classification systems for lung cancer show.

The proposed revisions (8th edition) of the TNM staging system for lung cancer gives more weight to tumor size as a prognostic factor, reclassifies some primary tumor (T) descriptors, validates current nodal status (N) descriptors, modifies the definition of some types of metastases (M), and includes additional stages for better prognostic stratification, reported Dr. Ramón Rami-Porta from the Universitari Mútua Terrassa in Barcelona, at a conference on lung cancer sponsored by the International Association for the Study of Lung Cancer.

Similarly, the updated World Health Organization (WHO) Classification of Lung Tumors, described by Dr. William D. Travis from the Memorial Sloan Kettering Cancer Center in New York, incorporates knowledge gained from immunohistochemistry and molecular testing for common genetic mutations into recommendations for treating the specific clinical circumstances of patients with lung cancer.

WHO’s Next

“The 2015 WHO Classification captures a remarkable decade of advances,” Dr. Travis said.

For surgically resected patients, the classification officially recognizes the first time subsets of non-small cell lung cancer of adenocarcinoma histology with survival rates of 100% (adenocarcinoma in situ), or nearly 100% (minimally invasive adenocarcinoma).

Among the major changes that will affect the diagnosis of surgically resected patients are the adoption of the 2011 IASLC/ATS/ERS Lung Adenocarcinoma Classification, restriction of a diagnosis of large cell carcinoma to tumors lacking clear differentiation by both immunohistochemistry and morphology, re-classifying of squamous cancers into keratinizing, nonkeratinizing, and basoloid subtypes with elimination of clear cell, small cell, and papillary subtypes. Neuroendocrine subtypes are grouped together, but their classification otherwise remains largely unchanged.

The revised classification is expected to improve prediction of survival and recurrence, predict whether a patient is likely to have a survival benefit with platinum-based chemotherapy, allow radiologic pathologic correlations, and affects TNM staging by emphasizing solid tumor size (vs. whole tumor size), Dr. Travis said.

TNM Changes

The proposed changes to the TNM tumor staging have been submitted for approval to the American Joint Committee on Cancer and the Union for International Cancer Control.

If adopted, they would represent the first significant changes since the 7th edition’s publication in 2009. The changes are based on data on more than 77,000 patients diagnosed with lung cancer from 1999 through 2010.

The proposed changes are not intended, however, to alter clinical practice, and instead “imply a taxonomic refinement rather than new indications of already established treatment protocols,” Dr. Rami-Porta said.

In some cases, the proposed changes would result in an upgrading of the T stage, while others would result in downgrading. For example, tumors that range in size between 1 and 2 cm, designated T1a in the 7th edition, would be T1b in the 8th edition. Similarly, tumors larger than 2 cm and up to 3 cm would be upgraded from T1b to T1c, those larger than 4 up to 5 would go from T2a to T2b, those larger 5 and up to 7 cm would rise from T2b to T3, and those larger than 7 cm would be reclassified from T3 to T4.

The changes imply a taxonomic refinement rather than new indications of established protocols.

The 2015 WHO Classification captures a remarkable decade of advances.’

The proposed revision would continue to group in the M1a category cases with pleural/pericardial effusions, contralateral/bilateral lung nodules, and distant metastases. Although they found no significant differences in survival among patients with M1a (metastases within the chest cavity) descriptors, when distant metastases outside the chest cavity (M1b) were assessed by the number of metastases, they found that patients with tumors with one metastasis in one organ had significantly better outcomes than those who had multiple metastases in one or more organs.

The proposed revision would then be M1b, and multiple lesions in a single organ or multiple lesions in multiple organs would be reclassified as M1c.
Recent quitters win big in lung screening trials

BY NEIL OSTERWEIL
Frontline Medical News

DENVER – It’s never too late to quit smoking, results of lung cancer screening trials confirmed. Among more than 3,300 heavy smokers over age 50 who took part in two low-dose CT (LDCT) screening programs, former smokers had a 37% reduction in all-cause mortality, compared with current smokers, and those who were active smokers at the time of randomization but quit during the follow-up period had a 43% lower risk for death, compared with those who continued to smoke, reported Dr. Ugo Pastorino of the Instituto Nazionale dei Tumori in Milan.

He noted that the U.S. National Lung Screening Trial (NLST) showed that screening with low-dose helical CT was associated with a nearly 7% reduction in all-cause mortality over a 7-year follow-up period, compared with patients screened with chest x-ray.

“But we have to keep clear in our minds that the benefit achieved by this trial of early detection in terms of mortality reduction is only 1% per year, so it’s a not a major improvement. “It’s a start, but we have to aim to improve this mortality reduction,” Dr. Pastorino said at a conference sponsored by the International Association for the Study of Lung Cancer.

Neither the NLST nor other randomized screening trials currently underway have examined in detail the effects of smoking status on screening outcomes, prompting Dr. Pastorino and his colleagues to investigate the matter in two cohorts of smokers assigned to LDCT in screening trials.

The study included 3,381 heavy smokers with a median follow-up of 9.7 years and a total follow-up of 32,858 person-years.

Men comprised 69% of the combined cohorts, who had a median age of 58 and a median smoking history of 40 pack-years.

The investigators divided the participants into current smokers — those who continued to smoke throughout the screening period, or if they quit did so within 1 year of the end of follow-up or death — and former smokers, subdivided into early quitters, who had stopped smoking by the time of accrual, and late quitters, who were active smokers at the time of accrual or randomization but stopped smoking at least 1 year before the end of the follow-up period or at least 1 year before death.

In an analysis of the effects of smoking on mortality, controlled for age, body mass index, lung function, and pack-years smoked, the investigators found that the relative risk for death from any cause among both early and late quitters, compared with current smokers, was 0.74.

When they excluded 239 quitters who had kicked the habit less than 2 years before the end of follow-up or death, the benefits of not smoking were even greater, with a relative risk of 0.61.

Interestingly, when they looked at the early quitters, compared with current smokers, the RR for quitting was 0.63, and the effect appeared even stronger among more recent (late) quitters, who had an RR for all-cause mortality of 0.57, compared with current smokers. (All comparisons were significant as shown by 95% confidence intervals.)

Also of note was the fact that lung cancer accounted for fewer than 30% of deaths, Dr. Pastorino noted.

Dr. Nise H. Yamaguchi of the Hospital Israelita Albert Einstein in Sao Paolo applauded Dr. Pastorino and his colleagues for the study, and succinctly summarized the take-home message:

“If you came here from all around the world to see all these fancy treatments and everything that you can’t do, go back home and help people stop smoking, because you cure lots of people and save many lives,” she said.

VITALS

Key clinical point: Quitting smoking results in a significant reduction in all-cause mortality among heavy smokers taking part in screening programs.

Major finding: Compared with current smokers, the relative risk for all-cause mortality among ex-smokers or recent quitters was 0.74.

Data source: Data on two cohorts totaling 3,381 current or ex-smokers assigned to low-dose CT lung screening.

Disclosures: The study was supported by the Italian Ministry of Health.

Share of lung cancer patients who never smoked is rising

BY SUSAN LONDON
Frontline Medical News

DENVER – An increasing share of patients with lung cancer report that they have never smoked, according to a pair of retrospective cohort studies reported at a world conference on lung cancer.

At three U.S. institutions serving geographically and racially diverse populations, the proportion of never smokers rose from 9% to 15% over a 24-year period among patients with non–small cell lung cancer (NSCLC), but did not change among those with small-cell lung cancer (SCLC). At a U.K. tertiary care institution, the proportion of never smokers rose from 13% to 27% over a 7-year period among patients undergoing surgery for lung cancer.

Data further suggested that these trends were due at least in part to an increase in the absolute number of never smokers with lung cancer, and not simply to a decline in the proportion of smokers with lung cancer, or to earlier, incidental detection of tumors resulting from better imaging technology.

More research will be needed to determine the specific factors driving this increase, according to Dr. Everett E. Vokes, cochair of the conference, moderator of a related press conference, and the John E. Ultmann Professor and Chair, department of medicine, University of Chicago.

“What is causing this, for me, would be very, very speculative,” Dr. Vokes said. “Secondhand smoke is still there, and radon is mentioned. That shouldn’t necessarily justify an increase, because those are either constant or also decreasing [like smoking]. And of course it could be pollution and factors that have to do with small particles and carcinogens in the air.”

In the first study, investigators led by Dr. Lorraine Pelosof of the University of Texas Southwestern Medical Center in Dallas used registries at three institutions — Southwestern Medical Center, Parkland Hospital in Dallas, and Vanderbilt University in Nashville, Tenn. — to identify patients who were diagnosed with lung cancer between 1990 and 2013.

Analyses were based on 10,593 patients with NSCLC and 1,510 patients with SCLC.

The latter serve as an internal control given cancer’s tight link with smoking, Dr. Pelosof noted.

In adjusted analyses, the proportion in the NSCLC group who reported never smoking increased from 9% to 15% during the study period ($P$ less than .0001). In contrast, the proportion in the SCLC group held steady at roughly 2%.

Among patients with NSCLC, never smokers were on average younger and more likely to be female, compared with smokers, Dr. Pelosof reported at the conference, which was sponsored by the International Association for the Study of Lung Cancer.

In teasing out the cause for the rise in never smokers with NSCLC, analyses showed that the absolute numbers of patients with NSCLC increased during the study period.

Preliminary data suggested that earlier, incidental detection did not explain the trend, as rates of
Continued from previous page

stage I, II, and III disease in never smokers were stable or decreased, while the rate of stage IV disease increased.

In addition, the trend did not appear to be explained by an influx to the institutions of patients with mutations seeking targeted therapies on clinical trials, as the trend persisted after adjustment for race/ethnicity, which was used as a surrogate for mutational status.

The investigators plan several avenues of additional research to sort this out, Dr. Pelosof said. “We want to look at possibly other institutions that are geographically and demographically diverse. Additional institutions would be helpful,” she said. “And then to get at some of the mechanisms, looking at mutational status and biology I think would be very important.”

In the second study, Dr. Eric Lim, a consultant thoracic surgeon at Royal Brompton Hospital, and a senior lecturer and reader in thoracic surgery at the National Heart and Lung Institute, Imperial College, London, and his colleagues assessed smoking status among 2,170 patients who underwent surgery for lung cancer at the hospital between 2008 and 2014.

Overall, 20% of the patients in the cohort were never smokers. Their mean age at presentation was 60 years, and two-thirds were women.

The predominant tumor types were adenocarcinoma, seen in 54%, and carcinoid, seen in 27%.

The proportion who were never smokers more than doubled during the study period, from 13% to 27%. The absolute annual number of such patients also rose, from about 60 to nearly 100.

Fully 52% of the never smokers presented with only nonspecific symptoms of cough or chest infection, while 11% had hemoptysis.

In the remaining 36%, the cancer was identified as an incidental finding on imaging done for other reasons.

“Nonsmoking lung cancer is increasing and now a significant proportion of the workload for surgeons across the United Kingdom,” concluded Dr. Lim. “Early detection in this group is challenging because they have no clear-cut symptoms, and serious symptoms were only present in a minority,” he said. “Clearly it’s not going to be cost effective to screen the entire population of nonsmokers for lung cancer,” he added. Since these patients “do not have established risk factors, research into early detection, ideally by noninvasive or molecular screening, is urgently required to identify early lung cancer in nonsmokers.”

Dr. Pelosof and Dr. Lim reported having no relevant financial conflicts of interest.
IOM: Teamwork key to reducing diagnostic errors

BY JULIE APPLEBY
Kaiser Health News

WASHINGTON – Almost every American will experience a medical diagnostic error, but the problem has taken a back seat to other patient safety concerns, an Institute of Medicine panel said in a report calling for widespread changes.

Diagnostic errors – defined as inaccurate or delayed diagnoses – account for an estimated 10% of patient deaths, hundreds of thousands of adverse events in hospitals each year, and are a leading cause of paid medical malpractice claims, according to the report.

Such errors can occur with very rare conditions, such as the Liberian man with undetected Ebola who was sent home from a Dallas hospital last September; or more common problems, such as acid reflux being...
Sustained effect. Control over 12 weeks.

Change in 2-hour postdose FEV1 over the 12-week study

- SYMBICORT 160/4.5 significantly improved predose FEV1 (P<.05 vs budesonide, formoterol, and placebo) averaged over the course of the study, and also improved 12-hour average postdose FEV1 (P<.001 vs budesonide, formoterol, and placebo at week 2), coprimary endpoints;
- 2-hour postdose FEV1 over 12 weeks was a secondary endpoint

*Week 12, last observation carried forward
†Baseline is defined as the predose FEV1 value on day of randomization
‡ Unadjusted P values based on treatment comparison of absolute mean change from baseline for SYMBICORT vs budesonide and placebo.
§ Administered as 2 inhalations twice daily.

• SYMBICORT 160/4.5 significantly improved predose FEV1, (P<.05 vs budesonide, formoterol, and placebo) averaged over the course of the study, and also improved 12-hour average postdose FEV1 (P<.001 vs budesonide, formoterol, and placebo at week 2), coprimary endpoints; 2-hour postdose FEV1 over 12 weeks was a secondary endpoint

The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis

The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection

SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents

Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma

ECG changes and/or hypokalemia associated with nonpotassium-sparing diuretics may worsen with concomitant beta-agonists.

Use caution with the coadministration of SYMBICORT to patients. It recommends better teamwork among health care providers, patients, and families. Citing the dearth of data about diagnostic errors, the report calls for voluntary efforts to report such problems. Dedicated funding is needed for research, the report says, and hospitals and doctors need to

Continued on following page
SYMBICORT® 80/4.5 (budesonide 80 mg and formoterol fumarate dihydrofumarate 4.5 mg) Inhalation Aerosol

SYMBICORT® 160/4.5 (budesonide 160 mg and formoterol fumarate dihydrofumarate 4.5 mg) Inhalation Aerosol

For best inhalation only

**WARNINGS AND PRECAUTIONS**

**Indications and Usage**

**Contraindications**

**Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.**

**Symptoms and signs of systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.**

**Inhalation suspension.**

**Asthma-Control Medication.**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**

**Asthma-Related Death**

**Long-acting beta 2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death.**

**Symptoms of adrenal insufficiency (e.g., nausea, vomiting, pain, abdominal pain, diarrhea, low blood pressure, weak pulse, sweating).**

**Worsened or Persistent Lower Respiratory Tract Infection:**
Making the systems more efficient and allowing patients to access their own medical records to check for and correct errors "could be a game changer," said Berenson. Indeed, patients "are going to be critical to the solution," said Dr. Michael Cohen, another report author and a professor of pathology at the University of Utah, Salt Lake City. "There's a real opportunity for patients to advocate for themselves and at the same time to challenge the health care providers about the diagnosis being made."

Helen Haskell, who formed Mothers Against Medical Error after her 15-year-old son died as the result of a medical error, said she was pleased the report focused on better teamwork and communication. She also said patients need better access to their records—which typically hospital officials said they always should ask questions.

"What else can it be? Does this diagnosis match all my symptoms?"

were two of the best questions to ask, said Haskell. "If there is any question, people should get a second opinion."

Kaiser Health News is a nonprofit national health policy news service that is part of the Henry J. Kaiser Family Foundation.
In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in breast milk in humans. Although the clinical significance of these effects in human breast milk is not known, cautions are advised in the use of SYMBICORT in mothers who are breastfeeding.

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, because the concomitant administration of these drugs and SYMBICORT could result in serious, possibly fatal, hyperpyrexia and delirium.

Formoterol can produce hyperpyrexia and delirium in patients with acute mountain sickness, chronic obstructive pulmonary disease, and hyperthyroidism. Therefore, formoterol should be used with caution in patients with these conditions.

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol is a beta-2 agonist and can produce hyperpyrexia and delirium in patients with acute mountain sickness, chronic obstructive pulmonary disease, and hyperthyroidism. Therefore, formoterol should be used with caution in patients with these conditions.

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]

Formoterol should be used with caution in patients with a history of cardiovascular disease, particularly those with a history of angina, hypertension, or hypotension.

Formoterol should be used with caution in patients with a history of gastrointestinal disease, particularly those with a history of peptic ulcer disease, hemorrhoids, or diverticulitis.

Formoterol should be used with caution in patients with a history of hepatic disease, particularly those with a history of liver disease or jaundice.

Formoterol should be used with caution in patients with a history of psychiatric disease, particularly those with a history of depression, anxiety, or agitation.

Formoterol should be used with caution in patients with a history of renal disease, particularly those with a history of renal failure, nephritis, or nephrotic syndrome.

Formoterol should be used with caution in patients with a history of thyroid disease, particularly those with a history of hyperthyroidism or hypothyroidism.

Formoterol should be used with caution in patients with a history of urological disease, particularly those with a history of prostate hyperplasia or bladder outlet obstruction.

Formoterol should be used with caution in patients with a history of vascular disease, particularly those with a history of peripheral arterial disease or venous thrombosis.

Formoterol should be used with caution in patients with a history of other serious medical conditions, particularly those with a history of serious falls, falls due toKA]
Value-based care poses new legal risks for doctors

BY ALICIA GALLEGOS
Frontline Medical News

The government’s push toward value-based care aims to fix a broken reimbursement system and improve quality of care for patients. But the new payment models also bring new legal risks for physicians, experts and antifraud officials warned.

“Novel payment methodologies may present new program integrity vulnerabilities,” Dr. Shantanu Agrawal, director of the center for program integrity at the Centers for Medicare & Medicaid Services, said at an American Bar Association meeting. “As they assume financial risk, providers are also assuming program integrity risk. Without adequate controls, provider-run systems may be relatively vulnerable.”

The Department of Health & Human Services plans to have 30% of Medicare payments in value-based payment structures by the end of 2016, and 50% by the end of 2018. The transition will be driven through investments in alternative payment models such as Accountable Care Organizations (ACOs), advanced primary care medical home models, bundled payments models, and integrated care demonstrations for Medicare and Medicaid patients.

At the end of 2014, value-based payments represented 20% of Medicare fee-for-service payments to providers, according to CMS data. The rate was fueled by government programs such as the Medicare Shared Savings Program (MSSP), Pioneer ACOs, the Bundled Payments for Care Improvement Initiative, and the Comprehensive Primary Care Initiative. Meanwhile, HHS is encouraging private payers, marketplace plans, Medicare Advantage plans, and state Medicaid programs to move in the same value-based direction.

With so many new regulations, mandates, and programs coming down the pipeline, physicians are likely not thinking about the legal dangers that may arise with alternative payment structures, said Mark S. Kopson, a health law attorney in Bloomfield Hills, Mich., and chair of the American Health Lawyers Association’s Payers, Plans, and Managed Care Practice Group.

Fee-for-service models can involve claims “about excess treatments and unnecessary services to drive up reimbursement,” Mr. Kopson said in an interview. “When you get into these [value-based] types of programs, it’s the exact opposite. The real threat is the withholding of necessary care in order to reduce expenses and therefore drive up those margins for the providers.”

To avoid such claims, physicians should ensure that their charts include the reasoning behind treatment decisions and a thorough record of why certain treatments were chosen and diagnoses were made, Mr. Kopson advised.

“Going forward, your charting better be completely accurate and detailed so that you don’t leave room for the government to make an argument that you should have provided this or that additional treatment,” he said.

Inaccurate reporting of enrollment data or financial information within new payment models could also land doctors in legal trouble, according to CMS officials.

Problematic reports, enrollee data, or other information physicians are required to submit to the government could be considered falsification and lead to False Claims Act violations.

“Providers are responsible for the information reported and should ensure that the appropriate checks and balances are in place that verify data is reported timely and accurately,” Tony A. Salters, a CMS spokesman, said in an interview. “For some models, providers must attest to the accuracy of this data. [To] report in-accurately could result in violations of federal laws.”

Physician-run payment models, such as doctor-led ACOs, may also draw legal scrutiny if physicians fail to prevent bad behavior by de facto partners. Physicians must ensure that all costs claimed by subcontractors, other providers, and suppliers who are paid from or authorized by the provider-run system, have been validated, Mr. Salters said.

“Doctors need to be aware that other entities who become new partners should hold themselves to the same high standards,” he said. “Providers should have basic financial mechanisms in place, with more sophisticated systems requiring more sophisticated methods,” to ensure validation.

CMS officials recommend doctors conduct independent audits of their accounts, manual validation of record system accuracy, and periodic verification of subcontractor claims to confirm the accuracy of claims and costs within new payment models.

These are “all routine steps that practitioners can take in their own offices but which are even more important when the doctor assumes responsibility for a larger scope of services,” Mr. Salters said.

Gaps in documentation surrounding bundled payments can be another legal land mine, Mr. Kopson noted. Adequate records of the care spectrum are essential to prevent accusations that care was not provided during a single episode of care, or over a specific period of time.

“You have to capture and document all the services you are delivering, and have accurate tracking in place for the entire continuum of care,” Mr. Kopson said.

The CMS recommends that physicians establish a strong compliance program to assist with antifraud controls of new payment systems. When creating or updating a compliance program, government officials said providers should consider the unique characteristics of the model in which they participate.

agallegos@frontlinemedcom.com
On Twitter @legal_med

This study provides important empirical evidence that ICU admission can benefit “low-risk” patients. It demonstrates that the value of intensive care extends beyond mere life support for patients with an acutely failing organ and instead includes all the organizational and human resources that comprise an ICU.

It would be tempting to use these results to justify more liberal ICU admission, but that would be untenable in this era of constrained health care resources. Rather than increasing ICU use, we should make general wards function more like ICUs. The task at hand is to study why intensive care saves lives, then use that information to make hospital care safe and effective for all patients, regardless of where in the hospital they are cared for.

Dr. Ian J. Barbash is in the division of pulmonary, allergy, and critical care medicine at the University of Pittsburgh. Dr. Jeremy M. Kahn is in the department of health policy and management at the university’s Graduate School of Public Health. Both Dr. Barbash and Dr. Kahn are also at the university’s Clinical Research, Investigation, and Systems Modeling of Acute Illness Center. Both authors reported having no relevant financial disclosures. They made these remarks in an editorial accompanying Dr. Valley’s report (JAMA. 2015;314:1240-41. doi: 10.1001/ jama.2015.11171).

Dr. Shantanu Agrawal, director of the CMS center for program integrity, said, “Without adequate controls, provider-run systems may be relatively vulnerable.”
Reduce lung function decline

Delay IPF progression with Esbriet

**Indication**

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

**Select Important Safety Information**

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

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

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

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

**Drug interactions:** Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.
Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used.

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment. The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

**Specific populations:** Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

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

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

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

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.

†Rank ANCOVA with lowest rank imputation for missing data due to death. Patients who died were counted in the ≥10% decline category.

‡Stable was defined as no decline in lung function.

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

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

CONTRAINDICATIONS
None.

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

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

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

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Liver Enzyme Elevations [see Warnings and Precautions]
- Photosensitivity Reaction or Rash [see Warnings and Precautions]
- Gastrointestinal Disorders [see Warnings and Precautions]

ESBRIET® (pirfenidone)

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 823 patients received 2403 mg/day of ESBRIET and 824 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials.

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

The most common adverse reactions with an incidence of ≥10% and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Adverse Reactions occurring in ≥10% of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Gastro-esophageal Reflux Disease</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Weight Decreased</td>
</tr>
<tr>
<td>Arthralgia</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 (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

Postmarketing Experience
In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval 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
Immunodeficiency

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST
ESBRIET® (pirfenidone)

**DRUG INTERACTIONS**

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

**Moderate CYP1A2 Inhibitors**

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

Concomitant CYP1A2 and other CYP Inhibitors

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

**CYP1A2 Inducers**

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

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects: Pregnancy Category C.**

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m² basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal dose of 1000 mg/kg/day).

**Nursing Mothers**

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

**Pediatric Use**

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

**Geriatric Use**

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

**ESBRIET® (pirfenidone)**

**Hepatic Impairment**

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration section 2.2 in full Prescribing Information]. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment [see Clinical Pharmacology section 12.3 in full Prescribing Information].

**Renal Impairment**

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

**Smokers**

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

**OVERDOSE**

There is limited clinical experience with overdose. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation. In the event of a suspected overdose, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

**PATIENT COUNSELING INFORMATION**

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

**Liver Enzyme Elevations**

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

**Photosensitivity Reaction or Rash**

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

**Gastrointestinal Events**

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

**Smokers**

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

**Take with Food**

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

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005 USA

All marks used herein are property of InterMune, Inc.
© InterMune, Inc. 2015. All rights reserved. ESB/021115/0037
Medicare hospital-related mortality down

BY RICHARD FRANKI
Frontline Medical News

Several measures of mortality declined among hospitalized Medicare fee-for-service beneficiaries from 1999 to 2013, a study showed.

Over that time period, in-hospital mortality dropped from 1.3% to 0.71%. Meanwhile, 30-day mortality declined from 2.16% in 1999 to 1.65% in 2013, and 1-year mortality slipped from 4.49% to 3.48% among 60,056,069 individuals aged 65 years or older who were enrolled in a Medicare fee-for-service plan for at least 1 month over the study period, reported Dr. Harlan M. Krumholz of Yale University, New Haven, Conn., and his associates.

The decline in mortality was accompanied by a drop in the number of hospitalizations, which went from more than 35,000/100,000 person-years of enrollment in 1999 to just under 27,000 in 2013. The number of beneficiaries admitted to the hospital at least once went down as well, from almost 22,000/100,000 person-years to more than 17,000, as did the number of hospitalizations that involved major surgery: 3,784/100,000 person-years in 1999 and 3,105 in 2013 (JAMA 2015;314:355-65).

Dr. Krumholz is supported by a grant from the National Heart, Lung, and Blood Institute.

agallegos@frontlinemedcom.com

Most physicians still work in small practices

BY RICHARD FRANKI
Frontline Medical News

While medical practice arrangements seem to have changed dramatically over the last 30 years, the majority of physicians still work in small practices, the American Medical Association reported.

In a 2014 AMA survey, almost 61% of respondents worked in practices of 10 or fewer physicians. That’s down from the 80% reported by the AMA in 1983, but it still qualifies as a majority. Over that same period, the proportion of physicians working in practices of 25 or more increased from 3% to 20%.

These changes in practice size were related to changes in practice ownership, the AMA noted. In 1983, the percentage of physicians who were the owners of their practices was 76%. In 2014, that number was 51%.

Looking at short-term data comparing the 2014 survey with one from 2012, the AMA found that the “share of physicians who worked directly for a hospital or in practices that were at least partially owned by a hospital increased from 29% in 2012 to 32.8% in 2014. Over that 2-year period, the share of physicians who were directly employed by a hospital increased from 5.6% to 7.2%, while the percentage of physicians who were in solo practice decreased from 18.4% to 17.1%.”

agallegos@frontlinemedcom.com

Task force proposes to replace ABIM’s 10-year MOC exam

BY ALICIA GALLEGOS
Frontline Medical News

A task force convened by the American Board of Internal Medicine has proposed replacing the board’s 10-year Maintenance of Certification exam with more meaningful assessments and exploring certification in specialized areas.

The Assessment 2020 Task Force, which convened in 2013 to evaluate the ABIM Maintenance of Certification (MOC) program, released its proposals in a report that aims to inform ongoing redesign of ABIM’s Certification and MOC programs, according to Dr. Richard J. Baron, ABIM president and CEO.

The independent task force includes representatives from ABIM leadership and experts in assessment, education, health care, and consumer advocacy. The task force recommends that ABIM focus MOC assessments on cognitive and technical skills, recognize specialization, and consider certification in specialized areas without requiring maintenance of underlying certificates. On that final recommendation, ABIM has already started such changes. In July, the board announced that no disciplines within its MOC program will require underlying certification and that all diplomates can choose the certifications they wish to maintain.

The task force also recommends that ABIM replace its 10-year secure exam with more frequent assessments. The assessments could be taken in a secure setting – possibly at home with remote authentication – with the potential for some portion to be open book but still timed.

“The Assessment 2020 Task Force members provided useful insights and recommendations that will be instrumental as we reshape certification to meet physicians’ and society’s changing needs,” Dr. Clarence H. Braddock III, chair of the ABIM board of directors, said in a statement. “We now need to hear constructive feedback from the internal medicine community on these recommendations, begin to determine their feasibility and develop implementation plans where needed.”

Dr. Wayne J. Riley, president of the American College of Physicians, said the college is hopeful that the new report will lead to positive changes that raise the MOC’s relevance and value to physicians and patients. “We remain committed to advocating for substantial and meaningful reforms to the ABIM MOC program,” he said in an interview.

agallegos@frontlinemedcom.com

On Twitter @legal_med
Important Safety Information for BREO 100/25 for COPD

There’s MORE TO ME than COPD.
(chronic obstructive pulmonary disease)

Indications
- BREO 100/25 is a combination inhaled corticosteroid/long-acting beta₂-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO 100/25 is the only strength indicated for COPD.
- BREO is NOT indicated for the relief of acute bronchospasm.

Important Safety Information for BREO 100/25 for COPD

<table>
<thead>
<tr>
<th>WARNING: ASTHMA-RELATED DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
- BREO is contraindicated for primary treatment of status asthmaticus or other acute episodes of 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
- BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma.
- BREO should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.

Please see additional Important Safety Information for BREO 100/25 throughout this advertisement.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for BREO 100/25 on the pages following this advertisement.
24-hour BREO 100/25 provided sustained improvement in lung function

**Primary endpoint:** BREO 100/25 provided a 220 mL improvement in weighted mean FEV₁ (0-24 hours) from period baseline vs placebo (P<0.001) at end of the 28-day treatment period

### SECONDARY ENDPOINT: SERIAL FEV₁ (0-25 HOURS) ASSESSED OVER 1 FULL DAY AT DAYS 28 AND 29

![Graph showing FEV₁ improvement over time](image)

<table>
<thead>
<tr>
<th>HOURS POSTDOSE</th>
<th>BREO (n=33)</th>
<th>PLACEBO (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>100</td>
<td>-100</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>6</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>8</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>12</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>16</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>20</td>
<td>800</td>
<td>700</td>
</tr>
<tr>
<td>22</td>
<td>900</td>
<td>800</td>
</tr>
<tr>
<td>24</td>
<td>1000</td>
<td>900</td>
</tr>
<tr>
<td>25</td>
<td>1100</td>
<td>1000</td>
</tr>
</tbody>
</table>

*Zero-dose administration time (between 6 and 10 AM). FEV₁ = forced expiratory volume in 1 second; LS = least squares.

A multicenter, randomized, double-blind, placebo-controlled, crossover study evaluated the effect of 28 days of treatment with BREO 100/25 on lung function over 24 hours in 54 patients (mean age: 57.3 years) with COPD. The primary endpoint was weighted mean FEV₁ (0-24 hours) at the end of the 28-day treatment period (period Days 28 and 29). This was calculated from predose FEV₁ (mean of –30- and –5-minute measurements) and postdose FEV₁ after 5, 15, 30, and 60 minutes and 2, 4, 6, 8, 12, 16, 20, 22, 23, and 24 hours. The secondary endpoint was serial FEV₁ (0-25 hours) at period Days 28 and 29.

At screening, patients had a mean postbronchodilator % predicted FEV₁ of 48.8%, a mean postbronchodilator FEV₁/FVC ratio of 52.9%, and a mean % reversibility of 8.8%.

In a separate 6-month lung-function study: a multicenter, randomized, double-blind, parallel-group study compared the effect of BREO 100/25 vs fluticasone furoate (FF) 100 mcg and vs placebo (each administered once daily by the ELLIPTA inhaler) on lung function in 1030 patients (mean age: 62.7 years) with COPD. For the co-primary endpoints, BREO significantly improved mean FEV₁ (0-4 hours) postdose on Day 168 by 120 mL vs FF† and 173 mL vs placebo (P<0.001 for both); and BREO demonstrated a greater difference in LS mean change from baseline in trough FEV₁ at Day 169 of 115 mL vs placebo (95% confidence interval [CI]: 60, 169; P<0.001); the 48 mL difference vs viitanterol (VI) 25 mcg† did not achieve statistical significance (95% CI: –6, 102; P=0.082).†

†At screening, patients had a mean postbronchodilator % predicted FEV₁ of 48.3%, a mean postbronchodilator FEV₁/FVC ratio of 47.6%, and a mean % reversibility of 15.9%.

†The weighted mean comparison of BREO with VI, the LABA component, was assessed to evaluate the contribution of VI to BREO. IC3s are not approved as monotherapy for COPD.

†The trough FEV₁ comparison of BREO with VI, the LABA component, was assessed to evaluate the contribution of FF to BREO. Viitanterol is not approved as monotherapy.

### Important Safety Information for BREO 100/25 for COPD (cont’d)

#### WARNINGS AND PRECAUTIONS (cont’d)

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

- Oropharyngeal candidiasis has occurred in patients treated with BREO. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

- An increase in the incidence of pneumonia has been observed in subjects with COPD receiving BREO. There was also an increased incidence of pneumonia resulting in hospitalization. In some incidences these pneumonia events were fatal. In replicate 12-month studies of 3255 subjects with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in subjects receiving BREO 100/25 (6% [51 of 806 subjects]), fluticasone furoate (FF)/viitanterol (VI) 50/25 mcg (6% [48 of 820 subjects]), and BREO 200/25 (7% [55 of 811 subjects]) than in subjects receiving VI 25 mcg (3% [27 of 818 subjects]). There was no fatal pneumonia in subjects receiving VI or FF/VI 50/25 mcg. There was fatal pneumonia in 1 subject receiving BREO 100/25 and in 7 subjects receiving BREO 200/25 (<1% for each treatment group).

- Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

- 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. Use caution in patients with the above because of the potential for worsening of these infections.

#### WARNINGS AND PRECAUTIONS

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

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

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

- If paradoxical bronchospasm occurs, discontinue BREO 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.

- Viitanterol 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.
In patients with a history of exacerbations

BREO 100/25 significantly reduced the annual rate of moderate/severe COPD exacerbations

**Primary Endpoint: Annual Rate of Moderate/Severe Exacerbations**

Mean annual rate of moderate/severe exacerbations

<table>
<thead>
<tr>
<th></th>
<th>BREO 100/25 (n=403)</th>
<th>VILANTEROL 25 mcg (n=409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>0.90*</td>
<td>1.14</td>
</tr>
<tr>
<td>Reduction</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>*P&lt;0.024</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Important Safety Information for BREO 100/25 for COPD (Cont’d)

**Warnings and Precautions (Cont’d)**

- Decreases in bone mineral density (BMD) 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 (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO and periodically thereafter.

- Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, 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.

**Adverse Reactions**

- In subjects with COPD, the most common adverse reactions (≥3% and more common than placebo) reported in two 6-month clinical trials with BREO 100/25 (and placebo) were nasopharyngitis, 9% (8%); upper respiratory tract infection, 7% (3%); headache, 7% (5%); and oral candidiasis, 5% (2%).

- In addition to the events reported in the 6-month studies, adverse reactions occurring in ≥3% of the subjects treated with BREO 100/25 in two 1-year COPD studies included back pain, pneumonia, bronchitis, sinusitis, cough, ophthalmoplegic pain, arthralgia, influenza, pharyngitis, and pyrexia.

**Drug Interactions**

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

- 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 the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.

- 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 electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.

**Use in Specific Populations**

- Use BREO with caution in patients with moderate or severe hepatic impairment. Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment. Monitor for corticosteroid-related side effects.

**References**

BREO® ELLIPTA® 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation

The following is a brief summary only and is focused on the COPD indication. See full prescribing information for complete product information.

1 INDICATIONS AND USAGE
1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

BREO 100/25 is indicated for the maintenance treatment of adult patients with chronic obstructive pulmonary disease (COPD) as monotherapy or as add-on therapy with long-acting muscarinic antagonists for maintenance of bronchodilation as needed in adults 18 years of age and older. BREO 100/25 should be used only in patients requiring regular inhaled maintenance bronchodilator therapy. BREO 100/25 has not been studied in patients with a history of severe exacerbations requiring hospitalization.

BREO 100/25 is not indicated for the relief of acute bronchospasm.

2 CONTRAINDICATIONS

The use of BREO is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required (see Warnings and Precautions [5.2]).
- Severe hypersensitivity to milk protein or any of the excipients (see Warnings and Precautions [5.11], Description [11]).

3 WARNINGS AND PRECAUTIONS

3.1 Asthma-Related Death

BREO, like other inhaled corticosteroids or long-term systemic corticosteroid therapy, is associated with an increased risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA use. LABAs, including vilanterol, which is an active ingredient in BREO, are associated with an increased risk of asthma-related death.

3.2 Deterioration of Disease and Acute Episodes

BREO should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. Patients who have deteriorating asthma should be instructed to discontinue the regular use of these drugs and to use them only as needed for symptomatic relief of acute asthma symptoms. When prescribing BREO, the healthcare provider should also prescribe an inhaled, short-acting beta-agonist for rapid relief of acute symptoms. Patients should have immediate access to parenteral corticosteroids, systemic corticosteroids, and other appropriate therapy for the supportive and symptomatic management of severe asthma episodes.

3.3 Excessive Use of BREO

In clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with BREO. If such infections develop, they should be treated with appropriate local or systemic antifungal therapy, and the patient should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in patients postoperatively or during periods of stress for evidence of adequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercortisolism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, BREO should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for maintenance of COPD or asthma symptoms should be considered.

3.4 Drug Interactions

BREO is used in combination with long-acting muscarinic antagonists. The concomitant use of LABAs and long-acting muscarinic antagonists is associated with an increased risk of systemic corticosteroid effects (i.e., glucocorticoid excess). Particular care should be taken in patients postoperatively or during periods of stress for evidence of adequate adrenal response.

3.5 Humoral and Hematologic Effects

Like other corticosteroids, BREO has the potential to suppress hypothalamic-pituitary-adrenal (HPA) axis function. Weakened immune response, infections, and deaths have been associated with such suppression. Symptoms of adrenal insufficiency may occur during or after interruption of systemic corticosteroids and may include nausea, vomiting, weakness, or hypotension. Systemic and local corticosteroid use may result in the following:

- Systemic corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.
- Systemic and local corticosteroid use associated with increased risk of hypoglycemia, osteoporosis, and cataracts.
- Systemic corticosteroid use associated with increased cardiovascular adverse effects (i.e., hypertension, angina, cardiac arrhythmia, myocardial infarction, cerebrovascular adverse effects, and increased mortality in some clinical trials).
- Systemic and local corticosteroid use associated with increased risk of bone mineral density (BMD) loss. Although BREO may control COPD or asthma symptoms during these episodes, in recommended doses it should be treated with appropriate local or systemic antifungal therapy while treatment with BREO is continued. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO. Predose reduction is accomplished by reducing the daily predose dose by 2.5 mcg on a weekly basis during therapy with BREO. Lung function (FEV1, or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

3.6 Adrenocorticotropin (ACTH) Stimulaton Test

Transfer of patients from systemic corticosteroid therapy to BREO may unmask allergic conditions previously suppressed by the systemic corticosteroids (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.12 Cardiovascular Effects

BREO may increase the risk of systemic corticosteroid effects associated with cardiovascular adverse effects, including angioedema, rash, and urticaria. Discontinue BREO if such reactions occur.

3.7 Concurrent Use of Oral or Systemic Corticosteroids

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol alone) had no effect on serum cortisol levels. A 12- to 10-fold higher systemic exposure to vilanterol (subjects treated with vilanterol 100 mcg) respectively) have been associated with clinically significant prolongation of the Gc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO, like other sympathomimetic agents, should be used with caution in patients with cardiovascular adverse effects, including hypertension, cardiac arrhythmias, and hyperglycemia.

5.3 Blood Pressure

Rhythm Changes in Bone Mineral Density

8.1 Bone Mineral Density

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemic corticosteroid effects associated with cardiovascular adverse effects, including angioedema, rash, and urticaria. Discontinue BREO if such reactions occur.

8.1 Blood Pressure

8.1.2 Hypertension

5.10 Paradoxical Bronchospasm

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

11.1 Pharmacokinetic Interactions

Effects of Fluticasone Furoate/Vilanterol on the Therapeutic Doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].

Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO should be observed carefully. Adverse systemic effects of inhaled corticosteroids are rare in patients treated with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].

5.10 Paradoxical Bronchospasm

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

11.1 Pharmacokinetic Interactions

Effects of Fluticasone Furoate/Vilanterol on the Therapeutic Doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].

Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO should be observed carefully. Adverse systemic effects of inhaled corticosteroids are rare in patients treated with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].

Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients treated with BREO should be observed carefully. Adverse systemic effects of inhaled corticosteroids are rare in patients treated with the therapeutic doses of BREO. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction [see Warnings and Precautions (5.9), Drug Interactions (7.1)].
8.5 Geriatric Use Based on available data, no adjustment of the dosage of BREO in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out. Clinical trials of BREO in COPD included 2,508 subjects aged 65 and older and 594 subjects aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Hepatic Impairment Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects (see Clinical Pharmacology (12.3) for full prescribing information).

8.7 Renal Impairment There were no significant increases in either fluticasone furoate or vilanterol exposure in subjects with severe renal impairment (C/GI less than 30 mL/min) with healthy subjects. No dosage adjustment is required in patients with renal impairment. [see Clinical Pharmacology (12.3) for full prescribing information].

10 OVERDOSAGE

No human overdosage data has been reported for BREO. BREO contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO. Treatment of overdosage consists of discontinuation of BREO together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardio 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)).

17 PATIENT COUNSELING INFORMATION

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

Asthma-Related Death

Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO, increase the risk of asthma-related death.

For acute symptoms

Inform patients that BREO is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta2-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Inform 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
- Increase in lung function as outlined by the physician

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

Do Not Use Additional Long-Acting Beta2- agonists

Inform patients not to use other LABA for COPD and asthma.

Local Effects

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

Pneumonia

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

Hypercorticism and Adrenal Suppression

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

Reduction in Bone Mineral Density

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

Gender Effects

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

Risks Associated with Beta2-agonist Therapy

Inform patients of adverse effects associated with beta2-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

Hyperglycemia, Renal Effects, Including Anaphylaxis

Adviser patients that hypoglycemia reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO. Inform patients to discontinue BREO if such reactions occur. There have been reports of potentially severe anaphylactic reactions with systemic beta2-agonists, including fatalities. Instruct patients to stop using the medication and seek medical care immediately if any of these signs or symptoms are present.

Local reactions

Inform patients that local reactions (e.g., burning, stinging, itching, dryness) at the site of administration may occur.

Local irritation

Inform patients that local reactions (e.g., redness, swelling, burning) at the site of administration may occur.
Docs could face faster false-payments return demands

BY ALICIA GALLEGOS
Frontline Medical News

In a novel decision, the U.S. District Court for the Southern District of New York has ruled that the 60-day clock to return overpayments to the government begins ticking when a health provider receives notice of a potential overpayment exists, not when an overpayment is conclusively ascertained.

Doctors should be concerned about the ruling, said Houston health law attorney Michael E. Clark, immediate past chair for the American Bar Association Health Law Section.

“This is a very troubling development because the judge has embraced the theory that certainty is not required as to what constitutes an identified overpayment,” Mr. Clark said in an interview. “Rather, knowledge can be established by recklessness under the facts. In short, practitioners must set up systems to alert them about potential overpayments so they can move quickly to avoid potentially ruinous False Claims Act liability.”

The Aug. 3 ruling in Kane v. Healthfirst is the first published decision to address the 60-day overpayment rule imposed under the Affordable Care Act and the Fraud Enforcement and Recovery Act (FERA). The rule requires that an overpayment be reported and returned by health providers within 60 days of the “date on which the overpayment was identified.” Health providers who retain an overpayment beyond that point are subject to liability under the False Claims Act (FCA).

In the Kane case, the federal government contends that three hospitals operated by Continuum Health Partners failed to report and return overpayments to Medicaid within 60 days of identification. Because of a computer glitch, Continuum billed both the government and a managed care organization for the same services, according to court documents. After the New York State Comptroller’s Office alerted Continuum to a possible overbilling, Continuum hired an employee, Robert P. Kane, to conduct an internal investigation into its billing. Mr. Kane – who was later fired – allegedly found 900 potentially improper Medicaid claims totaling $1 million, according to court documents. The government claims Continuum failed to repay the overpayments within 60 days and instead repaid only “small batches” of the affected claims over the next 2 years. Mr. Kane filed a whistleblower suit against Continuum, and the government intervened as a plaintiff.

But Continuum argued that the hospitals did not knowingly conceal the overpayments from the government, and that the overbillings had not been officially “identified.” The defendants were provided only notice of potential overpayments and did not identify instances where there is an established duty to pay money to the government, even if the precise amount due has yet to be determined.

“After the comptroller alerted defendants to the software glitch and approached them with specific wrongful claims, and after Kane put defendants on notice of a set of claims likely to contain numerous overpayments, defendants had an established duty to report and return wrongly collected money,” Judge Ramos said. “To allow defendants to evade liability because Kane’s email did not conclusively establish each erroneous claim and did not provide the specific amount owed to the government would contradict Congress’s intentions.”

In an email, a spokesperson for the defendants said the hospitals are disappointed with the judge’s decision and will continue to vigorously defend their case in court. Attorneys for the government did not return messages seeking comment.

The judge’s ruling is encouraging to the federal government and for plaintiffs who wish to sue health providers for overbilling violations, said Joel M. Androphy, a Houston plaintiff's attorney.

“This is going to open the floodgates for lawyers now as part of their false claim and reporting practices to let the courts know about overpayment issues,” Mr. Androphy said in an interview.

Defendants can no longer complain they were confused by the 60-day overpayment rule and the meaning of “identification,” he added. The judge’s ruling makes the regulation more clear and provides guidance to health providers about how the rule will be enforced, he said.

Washington health law attorney Robert T. Rhoad, however, disagreed that the opinion clarifies application of the 60-day overpayment rule. The decision does not provide the bright lines for compliance that providers expect and need. To protect themselves from litigation, physicians should take prudent steps to conduct an appropriate investigation if faced with actual or constructive notice of a possible overpayment, Mr. Rhoad said. Showing that they acted with due diligence could help doctors withstand future governmental or judicial scrutiny.

Medicare hospital costs down over last 6 months of life

BY RICHARD FRANKI
Frontline Medical News

Inpatient costs for Medicare patients over the last 6 months of life dropped 23% per death from 2009 to 2013, a study showed.

After adjustment for inflation, the average inpatient cost for patients aged 65 years and older who died was over $17,400 in 2009.

By 2013, Medicare spending in the last 6 months of life had dropped to just under $13,400.

The trend in spending was similar over the last 3 months of life and over the last month, but the declines – 18% for the last 3 months and 14.5% for the last month – were not as great, reported Dr. Harlan M. Krumholz of Yale University in New Haven, Conn., and his associates (JAMA. 2015;314(4):355-65).

The investigators noted that “approximately 60% of spending in the last 6 months of beneficiaries’ lives occurred during their final month.”

The analysis included 60,056,069 individuals who were aged 65 years or older who were enrolled in a Medicare fee-for-service plan for at least 1 month between 1999 and 2013.

Dr. Krumholz is supported by a grant from the National Heart, Lung, and Blood Institute.

---

Adjusted Medicare inpatient spending per death, 1999-2013

Notes: Based on data for 60,056,069 beneficiaries aged 65 years or older who were enrolled in the Medicare fee-for-service program for at least 1 month. Adjusted for inflation to 2013.

What constitutes proper practice in telemedicine?

For the last few months, family physician R. Russell Thomas Jr. has split his time between visiting patients at his practice in Eagle Lake, Tex., and treating children who reside more than 300 miles away in Sheffield, Tex., via telemedicine. His virtual tool belt includes an electronic stethoscope that enables Dr. Thomas to hear a patient’s heartbeat in real time and a high-definition camera to view and diagnose skin lesions.

The telehealth services are part of a new initiative at Rice Medical Center, a 23-bed, critical access hospital in rural Eagle Lake – population 3,700. Dr. Thomas has thus far used the technology to treat patients at an at-risk children’s academy and a local primary school. Soon, he and other physicians will also use telemedicine to consult with cardiologists and internists who practice 70 miles away in Houston.

“I look at telemedicine not so much as a practice like cardiology or orthopedics, but more [as] a tool like a percussion hammer or an otoscope,” Dr. Thomas said in an interview. “It’s a tool to practice whatever it is that you do.”

Dr. Thomas is far from alone. Analysts predict vast growth in the telemedicine industry in the coming years. The number of health providers offering telemedicine is expected to rise from 22% in 2014 to 37% in 2015, according to research by Towers Watson. Another report, by BCC Research, shows the global telehospital/clinic and telehome market is expected to reach about $43 billion in 2019, up from $19 billion in 2014.

The explosion of telemedicine is driven by two primary factors, said Dr. Joseph P. McMenamin, a Richmond, Va., attorney who specializes in medical malpractice defense and telemedicine.

“As a society, we are increasingly reliant upon and enamored of electronic methods of communication,” Dr. McMenamin said in an interview. “In one sense, it’s just part of a larger trend. The other, more specific reason, perhaps, is the widespread dissatisfaction with the way our health care system operates today. We are blessed in the United States to have some of the finest physicians in the world. … and then we have this terribly complex, burdensome system for getting people to where they need to be to get care. Telemedicine, by comparison, is quick, convenient, and relatively inexpensive.”

But for doctors, the practice of telemedicine is strewed with challenges. Barriers include reimbursement, licensing, malpractice, and regulation. Topping the barriers is a lack of uniform standards about practices. A key question: What constitutes the responsible use of telemedicine?

States have differing ideas. Some require a physical examination by a physician prior to telemedicine. Some allow that encounter to be conducted via telemedicine, while others mandate the visit is in-person. Alabama, Georgia, and Texas require an in-person follow-up visit after a telemedicine encounter, according to 2015 data from the American Telemedicine Association (ATA). Sixteen states and Washington, D.C., have informed consent requirements for telemedicine patients. Still other states have no defined rules for the practice of telemedicine.

To promote consistency and better usage, the Federation of State Medical Boards in 2014 issued a model policy to state medical boards about the recommended practice of telemedicine. The policy maintains that the same standard of care applied to face-to-face encounters be applied to telemedicine encounters, said Lisa A. Robin, chief advocacy officer for the Federation of State Medical Boards (FSMB). At least 29 state boards have telemedicine rules that are consistent with the model policy. Ms. Robin said in an interview.

“As telemedicine continues to evolve, we believe there must be a very strong focus on ensuring patient safety through sound policy making and regulatory practices,” she said.

From practice debate to court dispute

Medical specialty societies are beginning to weigh in on acceptable telehealth practices for doctors.

In July, the American Academy of Pediatrics issued guidance advocating that use of telemedicine for episodic care should be done within the context of the medical home and that fragmented telemedicine services should be avoided. Guidance issued by the American Medical Association makes it clear that physicians who prescribe using telemedicine need to first establish a patient-physician relationship. In September, the American College of Physicians (ACP) also issued policy in support of expanded telemedicine use, but cautioned the practice should be between a physician and patient who have an established relationship. The FSMB guidance also states that doctors should establish a relationship with patients before practicing telemedicine.

But how that relationship is created is up for debate. In Texas, disagreement over what creates a physician-patient relationship has led to litigation between national telemedicine company Teladoc and the Texas Medical Board.

The case centers on a medical board rule that requires physicians to have a face-to-face visit with patients before treating them through telemedicine. The relationship can be created through telemedicine at an established medical site, but it may not be established through an online questionnaire, email, text, chat, or telephonic evaluation or consultation.

Teladoc sued the medical board in April claiming the rule violates federal antitrust laws. Teladoc provides access to medical care via phone or interactive video and treats patients for nonemergency conditions. A judge halted the rule’s enforcement in May. The company sued to ensure patients have access to the same high-quality telehealth care they’ve received for decades, said Teladoc CEO Jason Gorevic.

“We have employers, health plans, and hospital systems who are coming to us because telehealth is a solution to access-to-care challenges as well as a mechanism to control the cost of care,” Mr. Gorevic said in an interview. “It was our responsibility and quite frankly, our obligation, to take action where they were regulations being adopted that were counter to the interests of patients, payers, and physicians in the state.”

In an April statement, Dr. Michael Arambula, president of the Texas Medical Board (TMB), said the rule represents the best balance of convenience and safety by ensuring quality health care for patients.

“The board recognizes that as technology evolves, so too must regulations governing telemedicine,” Dr. Arambula said in the statement.

“However, a telemedicine scenario that allows a physician to treat an unknown patient without any objective diagnostic data and no ability to follow up with the patient sacrifices the patient’s safety for convenience.”

The Texas Medical Association (TMA) supported the TMB rule. Dr. Thomas, a former TMB member who is active with the TMA, said the rule’s logic is simple.

“Without a face-to-face visit, ‘the doctor has no knowledge of the patient, except for what they tell you in that one encounter,’ he said in an interview. ‘There are no follow-up opportunities, no mechanism for further assessment. It’s episodic care at its worst.’”

However, Dr. Reed V. Tuckson, president of the American Telemedicine Association, stresses rules such as the Texas Medical Board’s are unnecessarily intrusive to doctors and diminish the range of possibilities for telemedicine care.

“We do not believe the restrictive covenants that are being applied by far too many state medical boards are appropriate.” Dr. Tuckson said in an interview. “We do not believe they should dictating to physicians the tools that they should be able to use in partnership with their patients to meet patients’ individual needs.”

agallegos@frontlinemedcom.com
President’s Report: American College of Chest Physicians in 2015: Bigger Tent and Bigger Team

By Dr. Curtis N. Sessler, FCCP

Creating in 1935, the American College of Chest Physicians (CHEST) has existed for 80 years and continues to excel at meeting the professional society needs of chest physicians in North America. However, my experience this past year as President of CHEST has reinforced my appreciation that our organization is much more to many individuals involved in the care of patients with diseases of the chest and related conditions. We have truly become a global professional society that focuses on serving all care providers and the entire health-care team. The Vision of CHEST speaks to these priorities clearly, “The American College of Chest Physicians is the global leader in advancing best patient outcomes through innovative chest medicine education, clinical research, and team-based care.” We’ve become a professional home for many and, accordingly, the tent has grown in size and diversity.

The Global Tent

While CHEST has had a presence well beyond North America for many years, we have developed a renewed emphasis on serving the needs of physicians around the globe. About 20% of our 18,700 members hail from countries other than the United States and Canada. Leaders from numerous countries provide important representation to the organizational structure of CHEST as Global Governors. The Chair and Vice-Chair of the Global Governors serve as important members of the Board of Regents, helping to shape the direction and strategic plan of the organization. At the member level, more and more exchange of information occurs on an electronic level, figuratively shrinking the world. The new CHEST membership model offers more options to suit the international member, who, for example, may prioritize receiving the CHEST Journal only electronically at a reduced rate.

Speaking of our flagship journal, CHEST has a robust global presence, with approximately 50% of published manuscripts being submitted by international investigators and authors. While receiving an English language version of CHEST electronically may be the approach taken by many, an exciting international connection is publication of international editions of CHEST in China, India, Italy, Mexico, the Middle East, and Spain.

The American College of Chest Physicians has long been a leader in providing face-to-face continuing medical education and scientific sessions. CHEST continues to partner with other international and regional professional societies in contributing to excellent medical meetings. In the past year, CHEST has endorsed and participated by providing speakers at meetings in Greece, Italy, Turkey, and Argentina, to name but a few. Even our annual scientific meeting in October has enjoyed locations outside of the United States, reflecting the prominent role our Canadian colleagues play in the organization, with CHEST 2015 in Montreal right around the corner. Continuing this approach, our annual meeting will be held in Toronto and Vancouver in the next half-dozen years.

Several decades after the last formal global CHEST-sponsored meeting was held, we relaunched the concept of CHEST World Congress (CWC) with a highly successful meeting in Madrid, Spain, in the spring of 2014. Next April, CHEST breaks new barriers by having CHEST World Congress 2016 in Shanghai, China. This comprehensive scientific and continuing education meeting will include a mix of didactic, live-learning/simulations, and research presentations. In the same year as CWC-Shanghai, the inaugural class of the first formal Pulmonary and Critical Care Medicine (PCCM) fellowship training programs in China will graduate. In a unique partnership, North American experts in graduate medical education from CHEST have partnered with leaders from the Chinese Thoracic Society (CTS) and from Chinese major medical centers to develop a robust formal fellowship curriculum and materials – a first for medical subspecialties in China. There are now PCCM fellowship programs in a dozen major teaching hospitals in China with more planned.

In other international efforts, CHEST continues to play a prominent role in efforts to improve lung health globally through membership in the Forum of International Respiratory Societies (FIRS). Recently, FIRS has become increasingly active and more visible as a prominent voice for lung health. FIRS has published a highly regarded roadmap to global lung health, provided experts to the World Health Organization (WHO) and the United Nations, published statements on electronic cigarettes and other issues, and helped to raise awareness about lung cancer and other respiratory conditions.

Finally, there is a rich tradition of support for care providers and patients in need, domestically and worldwide, through the philanthropic arm of CHEST – the CHEST Foundation. For example, over the years, the foundation has provided millions of dollars in grants and awards to individuals and organizations in support of their local efforts to improve healthcare delivery and education in challenging circumstances worldwide.

So, it is easy to see the rapidly expanding global footprint of CHEST, as we provide a professional societal home for many clinicians and scientists around the world and work diligently to improve lung health worldwide.

A Bigger Tent for a Bigger Team

The majority of CHEST members describe themselves as physicians who specialize in pulmonary disease or pulmonary and critical care medicine. The three pillars of CHEST medicine are pulmonary disease, critical care medicine, and sleep medicine. Much of the work of CHEST is related to clinical practice, clinical research, and medical education in these areas. Without a doubt, the American College of Chest Physicians is, and will continue to strive to be, the professional society home for these core groups of physicians working in these areas. Also, physicians in closely related disciplines, including intensivists, pediatric pulmonologists, thoracic surgeons, and cardiologists who manage diseases of the chest and critical care play important roles in CHEST. They have been, and continue to be, important members of the CHEST family, and their needs are consistently addressed.

Much of the emphasis of CHEST efforts has been on meeting the needs of the practicing clinician – whether in academic medicine or community practice. Also, central aspects of the mission of CHEST include the important roles of knowledge development and translation through support for clinical research, publication of original investigations and reviews, and development and dissemination of clinical practice guidelines. We have had a consistently strong emphasis on training the next generation of chest specialists with innovative programs directed toward fellowship-level trainees. A great example is the unique CHEST Challenge, pitting teams of fellows from various training programs in a series of exciting head-to-head knowledge-based competitions. Impressively, CHEST Challenge has been expanded to India, where an estimated 90% of PCCM fellows participate. I’m excited about the latest expansion of our membership model to extend beyond subspecialty fellows to include residents, students, and other trainees. I have met many students and residents who have attended our annual meeting and report having a tremendous experience. This expansion of our membership model represents an important investment in the future of the organization.

Recent trends in the practice of medicine emphasize the growing roles of a diverse group of care providers and the importance of the team in optimal care delivery. These concepts are enthusiastically embraced by CHEST. Nurse practitioners and physician assistants make up an increasingly important group of care providers referred to as advanced practice providers (APPs). These individuals are working hand in hand with physician colleagues and participate in continuing medical education that includes attending the annual CHEST meeting, attending board review courses, and joining in other live-learning events. CHEST is developing more opportunities for APP education and training, including a specially designed concentrated mix of didactic and simulation sessions focusing on the APP. Also, APPs are included in a new category of clinicians with advanced degrees who may qualify for FCCP status – an honor previously available only to physicians and PhDs.

Physician and APP providers are important members of the health-care team that also includes respiratory therapists (RT), nurses, clinical pharmacists, and other therapists and technicians. RTs have played prominent roles in CHEST for years and continue to be key contributors to advancing lung health. We are proud to offer the ability of RTs with advanced degrees and other qualifications to apply for FCCP status, reflecting our recognition of their...
CHEST Around the Globe

BY DR. MARK J. ROSEN, MASTER FCCP
Medical Director, CHEST

CHEST Collaborates With Chinese Physicians to Advance Pulmonary and Critical Care Medicine

With the goal of advancing our educational mission and our profession, CHEST continues to expand its collaboration with Chinese leaders in pulmonary, critical care, and sleep medicine in a variety of venues.

In July 2015, faculty representing CHEST and the Chinese Thoracic Society worked together to conduct the First Sino-American Respiratory Forum, a 2-day program in Beijing that focused on clinical features and management of COPD, sharing knowledge and experience among Chinese and CHEST faculty. We plan for this to be an annual event with a different general topic each year.

Our work to introduce pulmonary and critical care medicine (PCCM) as a new subspecialty in China is moving ahead; the first step is to establish fellowship training programs that use a common curriculum across 12 academic sites in China. In collaboration with our Chinese colleagues, eight programs based in Beijing, Shanghai, Changsha, Chengdu, and Guangzhou have been activated, with four more joining in the coming year. Each of the eight active sites were visited over the last year by members of the CHEST PCCM Steering Committee, chaired by Darcy D. Marciniuk, MD, FCCP, a Past President of CHEST. These visits are intended to observe the programs in action, to monitor progress with implementation, and to offer feedback on how to continue to improve the quality of training. We anticipate visiting the sites annually as part of a continuing evaluation process, offering interim assessments with audit of adherence to program requirements and fellows’ knowledge.

We look forward to the first “graduating class” in the fall of 2017.

Finally, plans are proceeding rapidly for CHEST World Congress 2016, April 15-17, in Shanghai. With the support of the Chinese Thoracic Society, this will be another outstanding CHEST educational experience for the global professional community. Co-chaired by Dr. Marciniuk and Dr. Chen Wang, FCCP, President of the Chinese Thoracic Society, the program has been developed by an international committee, designed to fulfill the goal of delivering practical clinical education in formats that include plenary sessions by global experts, panel discussions, interactive case-based sessions, and hands-on simulation activities.

We look forward to keeping you informed of our progress, and hope you will join us in Shanghai in April 2016.

Trainee Resource Hub

As a new feature, the Trainee Resource Hub provides trainee members with access to personal and professional resources tailored to each early career level.

These resources provide tools needed to become clinicians, scholars, and teachers, to foster active participation and progress in the CHEST community.

There are three distinct resource areas for fellows, medical students and residents, and those transitioning out of fellowship. We hope trainee members find this tool useful throughout their journey in the chest medicine industry.

Learn more at chestnet.org/traineehub.
INTRODUCING
CO-SUSPENSION TECHNOLOGY

THE NEW SCIENCE OF INTELLIGENT DELIVERY IN RESPIRATORY MEDICINE

Exploring a new formulation for inhaled drug delivery

A specially engineered, phospholipid carrier particle with multiple drug crystals
Visit Co-SuspensionParticles.com to Learn More

CO-SUSPENSION TECHNOLOGY

All images are for illustrative purposes only.

**Interventional Chest/Diagnostic Procedures**

**Brief update on molecular analysis from EBUS-TBNA specimens**

With the breakthroughs in molecular targeted therapies for non-small cell lung cancer (NSCLC), EBUS-TBNA remains well-suited to obtain material for mutation analysis (Am J Respir Crit Care Med. 2012;185[2]:1316). Techniques for maximizing material for mutation analysis via EBUS-TBNA have been described (J Thorac Oncol. 2011;6[1]:203) and are continually being refined. With a combination of EBUS and rapid on-site evaluation (ROSE), a minimum of four needle passes should be considered to provide adequate specimens for mutation analysis (Ann Am Thor Soc. 2013;10:636). This use of EBUS and ROSE may prevent a repeat invasive diagnostic procedure aimed at molecular profiling in at least 1 out of 10 patients with advanced lung cancer and reduces the risk of retrieving inadequate samples for mutation analysis (Chest. 2015;doi: 10.1378/ Epub ahead of print).

Targetable mutations such as EGFR, ALK, and ROS1 have FDA-approved treatments, while others are being studied to determine their clinical significance, particularly as it relates to the development of tyrosine kinase inhibitors (TKI) resistance. For example, some mutations have alternative mechanisms of signaling activation downstream of EGFR. The EGFR T790M mutation (the most common mechanism of drug resistance to TKIs) was recently shown to respond well to AZD9291 in patients with lung cancer who previously had disease progression during prior therapy with TKIs (N Engl J Med. 2015;372[18]:1698). MET gene encodes a transmembrane tyrosine kinase receptor, and aberrant MET activation in NSCLC has also been linked with acquired resistance to EGFR TKIs. Several MET inhibitors are being developed and tested as potential therapies for NSCLC (PLOS ONE. 2015;doi:10.1371).

An emerging role for EBUS is identifying programmed death-ligand 1 (PD-L1) expression on tumor cells in mediastinal lymph nodes. Although it is not a definitive predictive marker of response to PD-1 inhibitors like nivolumab (a human anti-PD-1 monoclonal antibody that works as an immune checkpoint blocker), this biomarker is the single factor most closely correlated with response to anti-PD-1 blockade (Clin Cancer Res. 2014;20[19]:5064). To apply an individualized treatment paradigm in advanced NSCLC, mutation analysis is now mandatory, and EBUS-TBNA is a cornerstone of this strategy. Perfecting techniques to maximize material obtained by EBUS-TBNA is becoming critically important as the role of this procedure expands to include evaluation of new clinically relevant biomarkers.

**Pediatric Chest Medicine**

**Is ARDS consistent across ages? Contemplating the new Pediatric Acute Lung Injury Consensus Conference (PALICC) guidelines**

A unique challenge of caring for children is the wide range of developmental and physiologic stages that influence the response to lung injury and infection. As they grow, children experience tremendous alveolar proliferation, changes in airway size and resistance, alterations in chest wall compliance, and development of collateral ventilation channels. Immune system development over time will also significantly affect children’s response to lung injury. When considering the complex pathophysiology of acute respiratory distress syndrome (ARDS), we must be cognizant that children are not merely “little adults.”

An emerging role for EBUS is identifying programmed death-ligand 1 expression on tumor cells in mediastinal lymph nodes. This biomarker is the single most closely correlated with response to anti-PD-1 blockade.

**Pulmonary Physiology, Function, and Rehabilitation**

**Sighing dyspnea: The pulmonaryologists’ fibromyalgia?**

Evaluating unexplained dyspnea represents a challenge for the pulmonologist. However, there is a common syndrome that should be considered in certain circumstances given its consistent historical findings and lack of physical and objective abnormalities.

Sighing dyspnea as a clinical syndrome was first thoroughly described by Dr. Charles Maytum in 1938 (Allergy. 1938;10[1]:50). Several years earlier, Dr. Doris Baker recorded her experience with “a disorder incorrectly described by patients as breathlessness” (Lancet. 1934;228:174). These historical reviews both describe “attacks of sighing breathing.”

In almost all cases, the patients use stereotypical phrases to describe their breathlessness. Characteristic descriptions include “an inability to obtain a satisfying breath” or “trouble getting in enough air.” Sighing respirations are noted during the clinical visit. Fatigue and exhaustion are common. Sighing dyspnea does not wake the patient once sleeping. Frequently, a patient will bring his hand to his midsternum and tap the chest at the point where air gets stuck. A sensation of chest tightness is often described, confusing the condition with asthma. Invariably, the most distressing symptoms occur at rest and improve with exertion. The poor correlation of symptoms with the degree of exertion distinguishes sighing dyspnea from other organic causes.

Like fibromyalgia, the cause of sighing dyspnea is unknown. Management revolves around exploring psychological stressors (anxiety and depression) and an adequate explanation of the condition and its benign course.

**Pulmonary Vascular Disease**

**Duel Drug Therapy for PAH**

Treatment options for pulmonary arterial hypertension (PAH) have increased, but the efficacy of combin-
While these questions require further study, it seems reasonable to consider this combination therapy as initial treatment in PAH with functional class II or III symptoms.

Although these results clearly favor up-front dual-drug therapy, a number of questions remain. First, it is unknown whether the agents used have synergistic or additive effects or if the probability of having a clinical failure event was lessened simply because two drugs increased the chance of having a response to one of them. Second, the lower rate of events in the combination group was driven primarily by hospitalization for PAH that has not been validated as a survival surrogate. Finally, it is unknown if the benefits observed are limited to the drugs used or if other PAH drug combinations are superior to monotherapy.

Dr. Corey E. Ventetuolo
Steering Committee Member
Dr. James R. Klinger, FCCP
Ex Officio

Reference

Thoracic Oncology

Generalizing the findings of the National Lung Screening Trial

In 2011, the landmark results of the National Lung Screening Trial (NLST) were published (N Engl J Med. 2011;365[5]:395). For individuals at high risk for lung cancer based on age and smoking history, screening with low-dose computed tomography (LDCT) was shown to reduce mortality by 20%. Since then, lung cancer screening programs have begun screening across the country especially since March of this year when CMS approved coverage for this service. However, there are some concerns as to the generalizability of the NLST because the participants in that study were younger, more educated, less ethnically diverse, and healthier than the average American who would qualify for lung cancer screening (J Natl Cancer Inst. 2010;102[23]:1771).

Through a grant from the CHEST Foundation, Dr. Nichole Tanner sought to examine these subsets of patients within the NLST. She presented her findings at CHEST 2014. Further analysis of the NLST data revealed that screening with LDCT reduced lung cancer mortality in all racial groups. However, this benefit was more pronounced in blacks (hazard ratio, 0.61 vs 0.86). When stratified by race, black smokers were twice as likely to die of lung cancer as were white smokers (HR, 4.10 vs 2.25).

While blacks benefited more from screening with LDCT, the demographics associated with an improvement in lung cancer survival were less commonly found in this population. The authors conclude that in order to realize reductions in mortality from lung cancer screening, tailored dissemination efforts are needed to meet the needs of this community (Am J Respir Crit Care Med. 2015;192[2]:200).

Dr. Nichole T. Tanner, FCCP
Steering Committee Member
Common ICD-10 Codes that will keep you up at night

This month, we present a couple of code categories that will become familiar to ICU doctors. This includes some of the codes for respiratory failure and for sepsis.

While you can find additional codes in the ICD-10-CM Official Guidelines for Coding and Reporting available at http://www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html that are pertinent to critical care medicine, these codes also serve to reiterate a couple of points.

First, in the J96 codes for respiratory failure, you see a number of “Excludes1” codes. Remember that this means that a J96 category code MAY NOT be used if you have also chosen one of the excludes1 codes.

A type 1 Excludes note is a pure excludes note. It means “NOT CODED HERE!!” An Excludes1 note indicates that the code excluded should never be used at the same time as the code above the Excludes1 note. An Excludes1 is used when two conditions cannot occur together, such as a congenital form vs. an acquired form of the same condition.

In the R65 category with the SIRS/Sepsis codes, you will notice the “code first” direction. This instructs the coder to use another code describing the cause of the SIRS/Sepsis prior to using a R65 category code.

In addition, there is a “code also” direction, which instructs the coder to add a code for any associated organ dysfunction. These instructions enhance the specificity of the coding process.

### J96 Respiratory failure, not elsewhere classified

**Excludes 1:**
- acute respiratory distress syndrome (J80)
- cardiopulmonary failure (R90.2)
- newborn respiratory distress syndrome (R22.0)
- postprocedural respiratory failure (J95.82)
- respiratory arrest (R09.2)
- respiratory arrest of newborn (P28.81)
- respiratory failure of newborn (P28.5)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J96.00</td>
<td>Acute respiratory failure, unspecified whether hypoxia or hypercapnia</td>
</tr>
<tr>
<td>J96.01</td>
<td>Acute respiratory failure with hypoxia</td>
</tr>
<tr>
<td>J96.02</td>
<td>Acute respiratory failure with hypercapnia</td>
</tr>
<tr>
<td>J96.10</td>
<td>Chronic respiratory failure</td>
</tr>
<tr>
<td>J96.11</td>
<td>Chronic respiratory failure, unspecified whether hypoxia or hypercapnia</td>
</tr>
<tr>
<td>J96.12</td>
<td>Chronic respiratory failure with hypoxia</td>
</tr>
<tr>
<td>J96.20</td>
<td>Acute and chronic respiratory failure</td>
</tr>
<tr>
<td>J96.21</td>
<td>Acute and chronic respiratory failure with hypoxia</td>
</tr>
<tr>
<td>J96.22</td>
<td>Acute and chronic respiratory failure with hypercapnia</td>
</tr>
<tr>
<td>J96.90</td>
<td>Respiratory failure, unspecified whether hypoxia or hypercapnia</td>
</tr>
<tr>
<td>J96.91</td>
<td>Respiratory failure, unspecified with hypoxia</td>
</tr>
<tr>
<td>J96.92</td>
<td>Respiratory failure, unspecified with hypercapnia</td>
</tr>
</tbody>
</table>

### R65 Symptoms and signs specifically associated with systemic inflammation and infection

<table>
<thead>
<tr>
<th>Code first</th>
<th>Systemic inflammatory response syndrome (SIRS) of non-infectious origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excludes 1</td>
<td>underlying condition, such as: heatstroke (T67.0)</td>
</tr>
<tr>
<td>injury and trauma (S00-T88)</td>
<td></td>
</tr>
<tr>
<td>sepsis - code to infection</td>
<td></td>
</tr>
<tr>
<td>severe sepsis (R65.2)</td>
<td></td>
</tr>
</tbody>
</table>

| R65.10 | Systemic inflammatory response syndrome (SIRS) of non-infectious origin without acute organ dysfunction |
| R65.11 | Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction |
| Code first | use additional code to identify specific acute organ dysfunction, such as: acute kidney failure (N17.) |
| acute respiratory failure (J96.0) |
| critical illness myopathy (D72.81) |
| critical illness polyneuropathy (G62.81) |
| disseminated intravascular coagulopathy (DIC) (D65) |
| encephalopathy (metabolic) (septic) (G93.41) |
| hepatic failure (K72.0) |

| R65.20 | Severe sepsis without septic shock |
| R65.21 | Severe sepsis with septic shock |

**For more information, see:** http://www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html

---

**This Month in CHEST: Editor’s Picks**

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

**EDITORIAL**
A Paradigm Shift in the Treatment of Central Sleep Apnea in Heart Failure. By Drs. R. Mehra and D. J. Gottlieb.

**POINT AND COUNTERPOINT**
Should Childhood Vaccination Against Measles Be a Mandatory Requirement for Attending School?

Yes – Drs. R. D. Silverman and K. S. Hendrix

No – Drs. P Schroder-Back and K. Martakis

**ORIGINAL RESEARCH**
Dedicated Severe Asthma Services Improve Health-Care Use and Quality of Life. By Dr. D. Gibeon, et al.

Will Nonasthmatic Eosinophilic Bronchitis Develop Into Chronic Airway Obstruction? A Prospective, Observational Study. By Dr. K. Lai, et al.

ALABAMA

LUNG CENTER
Comprehensive Pulmonary/CCs of Care Medicine

SEeks A PULM/CC PHYSICIAN IMMEDIATELY!
- EBUS ultrasound
- Super Dimension Bronchoscopies
- Teaching opportunities through UAB
- Established, hospital-owned practice
- Employment w/excellent compensation package
- Medical, Surgical/Trauma, Neurological and Cardiovascular ICUs
- Level I Trauma/Regional Referral Center
- 20-25 patients/half day
- Huntsville named in Forbes list of Top Ten Smartest Cities in the World

Interested physicians should contact:
Kimberly Salvail
Huntsville Hospital
kimberly.salvail@hhsys.org
256-265-7073

Pulmonology/Intensivist
Join eight university trained, Board Certified Pulmonary, Critical Care and Sleep Medicine physicians. Our integrated multi-specialty physician clinic and hospital includes a Level II Trauma Center and an accredited sleep center. Practice with strong colleagues in the region’s tertiary referral center.

Physician-Led Medicine in Montana
Billings Clinic is nationally recognized for clinical excellence and is a proud member of the Mayo Clinic Care Network. Located in the magnificent Rocky Mountains in Billings, Montana, this friendly college community has great schools, safe neighborhoods and family activities. Exciting outdoor recreation minutes from home. 300 days of sunshine!

Contact: Rochelle Woods
1-888-554-5922
physicianrecruiter@billingsclinic.org

Billings Clinic

Fort Collins, Colorado
Colorado Health Medical Group is seeking a Pulmonologist/Critical Care trained physician. Sleep Medicine training desirable but not required. Will rotate in two hospitals and our Loveland based clinic. Call is 1:11 nights and 1:5-6 weekends. Physician will be doing general Pulm/CC procedures and read sleep studies from outlying facilities.

If interested, email your CV to Briann.Leone@uchealth.org

Disclaimer
Chest Physician assumes the statements made in classified advertisements are accurate, but cannot investigate the statements and assumes no responsibility or liability concerning their content. The Publisher reserves the right to decline, withdraw, or edit advertisements. Every effort will be made to avoid mistakes, but responsibility cannot be accepted for clerical or printer errors.
Catching Up With Our Past Presidents

Susan K. Pingleton, MD, Master FCCP
President: 1999-2000

My induction as President in Chicago coincided with the College’s 65th birthday anniversary, so it was quite a celebratory event. Memories of my year as President include interesting travels to the Philippines, India, Germany, Italy, and Canada to meet our international colleagues and friends. Challenges included the College’s first attempts to clarify any conflict of interest in our consultants and committee members resulting in the current conflict of interest disclosure requirements.

Since that time, I have been fortunate to have a continually evolving, demanding but very interesting professional life. After Division Director, I had the great honor to serve as Chair of Internal Medicine at the University of Kansas. That job provided quite a professional challenge, as well as education for me. Afterwards, on sabbatical leave, I spent a year in Washington, DC, at the Association of American Medical Colleges as the Petersdorf Fellow, learning much about health-care policy, as well as the health-care organization in DC that guides that policy. That education was capped off by a year at the University HealthCare Consortium in Chicago as the Chief Learning Officer.

Returning home to KU, I have been involved in mentoring, both junior physicians and health-care teams. I’ve conducted a year-long oral history study of KU female professors here at KU. As I reflect back on my working with the College for many years, cumulating in the Presidency, the American College of Chest Physicians provided me with essential leadership tools that have been extensively ever since. The College has provided great value, as well as great lifetime friendships for me, for which I am most grateful.

Mount Nittany Health Pulmonologist Opportunity

Position Highlights include:

Mount Nittany Physician Group currently provides a range of pulmonary medicine services including interventional procedures, allergy/immunology, and sleep medicine.

* Established practice with 6 physicians and growing patient demand within an expanding health system
* Mix of outpatient pulmonary medicine/procedures and inpatient pulmonary consults.
* Fully integrated EMR, electronic documentation and order entry
* Limited intensivist work available if desired, not required

Mount Nittany Medical Center, located in State College, PA, is a not-for-profit, 260 bed, acute care facility housing both inpatient and outpatient medical/surgical services. It is a growing and thriving facility offering unparalleled patient-focused care made all the more distinctive by excellent physicians, ease of access and facilities and systems engineered for the best in patient care.

State College, home to Penn State University, is a vibrant college town. It offers a diverse culture, a beautiful environment, excellent public and private schools, countless options for dining, theatre, sports and recreation, nightlife and more. This is all located within a safe, friendly community that makes the area perfect for raising a family. University Park Airport is located only five miles from town and State College offers easy access to Interstates 80 and 99.

Shelly Palumbo
Physician Recruiter
State College, PA
(814)231-6892 or (814)558-6223
michele.palumbo@mountnittany.org
www.mountnittany.org
Quit smoking after MI: Less angina, good mental health

BY KARI OAKES
Frontline Medical News

Patients who stopped smoking after their heart attack had less chest pain and experienced better mental health than did those who continued to smoke at 1 year after their acute myocardial infarction (AMI).

Moreover, the post-MI quitters had levels of angina and mental health similar to those who had never smoked, and scores improved with the passage of time after smoking cessation, according to a prospective, multicenter study.

Smoking cessation after a heart attack reduces mortality and the risk of recurrent MI by up to 50%, according to Donna Buchanan, Ph.D., and her coinvestigators.

However, few high-quality studies to date have examined the effect of smoking cessation on overall health-related quality of life (HRQOL), she said.

For this study, Dr. Buchanan and her colleagues used data from two large multicenter AMI registries to address how smoking status after AMI is related to mental and physical health status. Using the Seattle Angina Questionnaire and the Medical Outcomes Study Short Form 12-item questionnaire, investigators tracked changes in chest pain and mental and physical health status at 1, 6, and 12 months post AMI according to smoking status.

The final cohort included 4,003 patients who were then grouped by smoking status.

Patients were grouped into never smokers (1,145), former smokers (1,374), and current smokers. A total of 1,484 patients were smokers at baseline; of those, 801 were still smoking at 1 year post MI. The remaining 683 patients quit within the year after their AMI and were classified as recent quitters. In unadjusted analysis, never smokers had the highest health status scores and current smokers the lowest, with a gradation across the four categories of smoking status that was statistically significant for all domains, said Dr. Buchanan of the University of Missouri–Kansas City.

Further statistical exploration with multivariable analysis showed that former smokers and never smokers looked similar in all HRQOL, while there was more variability across HRQOL domains for recent quitters. Recent quitters were significantly more likely to report good mental health status than current smokers, even when levels of depression and social support were taken into consideration (Circ Cardiovasc Qual Outcomes. 2015 Aug 25; doi: 10.1161/circoutcomes.114.001545).

An examination of physical symptoms revealed that recent quitters had levels of angina similar to those who had never smoked, while persistent smokers had more angina post AMI than any other group. Dr. Buchanan and her colleagues noted that the oxidative stress, endothelial damage, and inflammatory state that are caused by smoking all may contribute to ongoing angina. Smokers also experience increased adrenergic tone, and may have more coronary vasospasm.

The study was funded by CV Therapeutics and the National Institutes of Health. A coinvestigator owns the copyright to the Seattle Angina Questionnaire, used to assess angina in the study.

koakes@frontlinemedcom.com
On Twitter @karioakes

SPRINT shows lives saved with lower systolic BP

BY KARI OAKES
Frontline Medical News

Deaths were reduced by nearly one-quarter when systolic blood pressure was treated to a target of 120 rather than 140 mm Hg, according to a large National Institutes of Health-sponsored study comparing standard blood pressure treatment with more-intensive lowering of systolic blood pressure. The lower blood pressure group also saw a 30% reduction in the composite primary endpoint of cardiovascular events, stroke, and cardiovascular death.

The magnitude of the effect of the lower blood pressure target prompted the study’s data safety monitoring board to end the study early, said officials from several NIH agencies at a telebriefing. The study was unblinded in August 2015, and a full report of the primary outcome measures will come in a paper due out by the end of the year, they said.

The Systolic Blood Pressure Intervention Trial, or SPRINT, is a 100-site trial that enrolled more than 9,100 people in the United States and Puerto Rico aged at least 50 years with high blood pressure and at risk for cardiovascular disease; those with diabetes were excluded. Patients were randomized to a standard treatment target of 140 mm Hg or less, or to a more intensive 120 mm Hg.

SPRINT participants received evidence-based treatment with a variety of antihypertensives, with the intervention arm requiring an average of almost three medications, compared with just under two for the less-intensive treatment arm.

Against a backdrop of uncertainty in the literature about what the target systolic blood pressure should be for those with hypertension and at risk for cardiovascular events or kidney disease, the study provides compelling evidence that more-aggressive blood pressure lowering is important. “More-intensive management of blood pressure can save lives,” said Dr. Gary Gibbons, director of the National Heart, Lung, and Blood Institute. This is good news, he said, since about one in three Americans has high blood pressure, and only about half of those 70 million currently have their blood pressure under control.

Dr. Jackson T. Wright Jr., SPRINT study lead and director of the clinical hypertension program at Case Western Reserve University in Cleveland, also emphasized that intensive blood pressure management can prevent the cardiovascular complications of hypertension. Though subgroup analysis is ongoing, he said, SPRINT, he said, also “offers an excellent opportunity to examine the tolerability and safety of the lower target.” The first look at the safety data shows that the more-intensive treatment is well tolerated, though data analysis is ongoing, he said.

Dr. Suzanne Oparil, director of the vascular biology and hypertension program at the University of Alabama–Birmingham, said, “This is a time of enlightenment.” The previous absence of compelling data played a part in the debate surrounding blood pressure levels that should be used in guidance documents, and Dr. Gibbons and Dr. Wright both emphasized that they would expect the forthcoming primary outcomes paper to have an impact on guideline-writing bodies. Dr. Wright said, however, “We are not providing guidance for providers or patients right now. The study was just unblinded a little less than 3 weeks ago.”

In 2014, the group of experts who had constituted the JNC 8 panel, a team assembled in 2008 by NHLBI to update official U.S. hypertension management guidelines, set the target blood pressure for the general population aged 60 years or older to less than 150/90 mm Hg, a major break from long-standing practice to treat such patients to a target systolic pressure of less than 140 mm Hg (JAMA. 2014;311[5]:507-20). These guidelines, released after SPRINT began, remain controversial.

The SPRINT MIND trial, tracking the relationship between systolic blood pressure and cognitive impairment or dementia, is ongoing. The study is also still collecting data about kidney function in study participants.

The study was funded by the National Institutes of Health. Two drug companies, Takeda and Arbor, provided some medication for the trial.

koakes@frontlinemedcom.com
On Twitter @karioakes
INDICATION AND USAGE
REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in adults to improve exercise ability and delay clinical worsening. Exercise ability was demonstrated when REVATIO was added to background epoprostenol therapy.
Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and idiopathic pulmonary hypertension (71%) or associated with connective tissue disease (CTD) (25%).

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

DOSEAGE AND ADMINISTRATION
REVATIO Tablets and Oral Suspension
The recommended dose of REVATIO is 5 mg or 20 mg three times a day.

Reconstitution of the Powder for Oral Suspension
Tap the bottle to release the powder.
Remove the 7.5 mL (50 mg) glass vial stopper. Replace the cap on the bottle.

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 put the water into the bottle.
4. Place the cap and shake the bottle vigorously for a minimum of 30 seconds.
5. Remove the cap, 6. Accurately measure out another 30 mL of water and add this to the bottle. You should always add a total of 90 mL of water irrespective of the dose prescribed.
7. Replace the cap and shake the bottle vigorously for a minimum of 30 seconds.
8. Remove the cap. 9. Press the bottle adapter into the neck of the bottle.

Reconstitution of the Powder for Oral Suspension
The adapter is provided so that you can fill the oral syringe with medication from the bottle. Replace the cap on the bottle. 10. Write the expiration date of the constituted oral suspension on the bottle label (the expiration date of the constituted oral suspension is 60 days from the date of constitution).

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

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

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

Hypotension
REVATIO has vasoactive 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 vasoactive effects (e.g., patients on antihypertensive therapy or with resting hypotension [BP less than 90/50], fluid depletion, severe left ventricular outflow obstruction, or automatic dysfunction). Monitor blood pressure when co-administering blood pressure lowering drugs with REVATIO.

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

Epiptaxis
The incidence of epiptaxis was 13% in patients taking REVATIO with PAH secondary to CTD. This effect was not seen in idiopathic PAH (REVATIO 3%, placebo 2%) patients.

Seizure
Sleep-related transient episodes of apnea with increased respiratory rate have been observed in patients receiving REVATIO.

Visual Loss
When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vasculare risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disk”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. Based on published literature, the annual incidence of NAION is 2.5–11.8 cases per 100,000 males aged ≥50 year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION in otherwise healthy males. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including REVATIO. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors. There are no controlled clinical data on the safety or efficacy of REVATIO in patients with retinitis pigmentosa, a minority who have genetic disorders of retinal phosphodiesterases. Prescribe REVATIO with caution in these patients.

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo, % (n=70)</th>
<th>REVATIO 20 mg three times a day, % (n=69)</th>
<th>Placebo-Subtracted, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>30</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dysepsa exacerbated</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sinusits</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

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

The incidence of retinal hemorrhage with REVATIO 20 mg three times a day was 1.4% versus 0.2% placebo and for all REVATIO doses studied was 1.9% versus 0.1% placebo. The incidence of eye hemorrhage at both 20 mg three times a day and at all doses studied was 1.4% for REVATIO versus 1.4% for placebo. The patients experiencing these reactions had risk factors for hemorrhage including concurrent anticoagulant therapy.

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

Cardiovascular Events
In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhage, 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 taking sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to other risk factors.

Nervous system
Seizure, seizure recurrence.

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

Ritonavir and other Potent CYP3A4 Inhibitors
Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended.

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

Brief Summary of Prescribing Information.
Other drugs that reduce blood pressure Alpha blockers. In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope. Amlodipine. When sildenafil 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis).

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

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

Pediatric Use No dose adjustment for mild to moderate hepatic impairment. No dose adjustment for mild to moderate renal impairment is required. Severe impairment has not been studied.

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

PATIENT COUNSELING INFORMATION

• Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

• Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction. Advise patients taking REVATIO not to take VIAGRA or other PDE-5 inhibitors.

• Advise patients to seek immediate medical attention for a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

• Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

Rx only  
Rev. June 2015

RVU51714-02 ©2015 Pfizer Inc. All rights reserved. June 2015

Pfizer
REVATIO® (sildenafil) — is now available as an oral suspension treatment for PAH

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%).

Adverse events were generally transient and mild to moderate. Adverse events of REVATIO injection were similar to those seen with oral tablets.

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

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

No dose adjustment required for renal impaired.

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

Indication

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

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