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Pneumonia shifting from bacterial to viral etiologies

Trend due to vaccines, limits of testing.

BY M. ALEXANDER OTTO
Frontline Medical News

Viral infections appear to be the primary cause of pneumonia that results in hospitalization, according to a Centers for Disease Control and Prevention study of five urban hospitals in Chicago and Nashville, Tenn.

From January 2010 through June 2012, 2,259 patients hospitalized for community-acquired pneumonia (CAP) had both radiographic evidence of disease and specimens for bacterial and viral testing. A pathogen was detected

in just 853 (38%). One or more viruses were detected in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and fungal or mycobacterial pathogens in 17 (1%). The findings indicate the annual incidence of community-acquired pneumonia requiring hospitalization is about 25 cases per 10,000 adults, with the highest rates among adults 65-79 years old (63 cases per 10,000) and 80 years or older (164 cases per 10,000).

The most common pathogens were rhinovirus in 9% of patients, influenza virus in 6%, and *Strepto-*
See CAP etiology • page 9

Pediatric pulmonary HT is rising

BY DOUG BRUNK
Frontline Medical News

Between 1997 and 2012, the proportion of hospitalizations in the United States for pediatric pulmonary hypertension doubled, from 1 in 1,000 discharges for the condition in 1997 to 1 in 500 in 2012, a national retrospective cohort study found.

“These results have practice and policy implications at the institutional, state, and national levels, particularly in the face of increasing pressure to restrain costs while caring for a population with increasingly complex medical needs,” researchers led by Dr. Bryan G. Maxwell reported in *Pediatrics* (doi/10.1542/peds.2014-3834). Dr. Maxwell of the de-

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Ivacaftor + lumacaftor approved for CF

BY ELIZABETH MEHCATIE
Frontline Medical News

The fixed-dose combination of ivacaftor and lumacaftor has been approved by the Food and Drug Administration for the treatment of cystic fibrosis in people aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. This is the first drug treatment approved for people who have two copies of this mutation, the most common type of cystic fibrosis.

The approval broadens the availability of targeted treatments for the specific defects that cause cystic fibrosis,” Dr. John Jenkins, director of the

Office of New Drugs in the FDA Center for Drug Evaluation and Research, said in a statement.

About half of the approximately 30,000 people in the United States who have cystic fibrosis are homozygous for the F508del, the most common CF mutation, according to the FDA.

The combination contains 200 mg of lumacaftor and 125 mg of ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator; two pills are taken twice a day. It will be marketed as Orkambi by Vertex Pharmaceuticals. Ivacaftor, marketed as Kalydeco by Vertex, was approved in January 2012 for treating

See CF drug • page 10

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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 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.



Patient dramatization

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 prostanoids¹

- SERAPHIN included both incident (recently diagnosed) and prevalent (previously diagnosed) patients³
- Overall, the median time from diagnosis was 15 months, ranging from 1 day to 36 years³
- 25% of patients were diagnosed less than 6 months prior to enrollment in the study³

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 $>3 \times \text{ULN}$ was 3.4% for OPSUMIT vs 4.5% for placebo, and $>8 \times \text{ULN}$ 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 $>2 \times \text{ULN}$, 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.

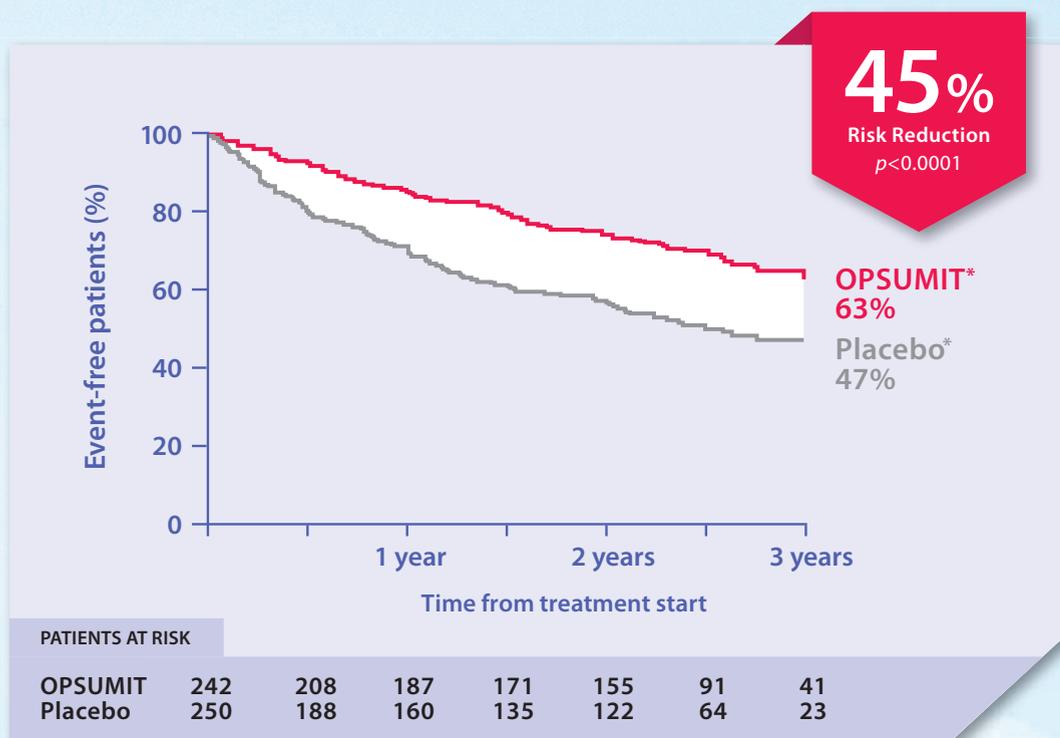
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macitentan tablets 10 mg

INDICATION

OPSUMIT® (macitentan) 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.

Keep disease progression in mind from the start of therapy: OPSUMIT is the only ERA approved to delay disease progression in FC II and III patients¹

Kaplan-Meier estimates of risk of first primary endpoint event in SERAPHIN



Disease progression included: death, initiation of IV or SC prostanoids, or clinical worsening of PAH (decreased 6MWD, worsened PAH symptoms and need for additional PAH treatment).¹

*Patients on PAH-specific background therapy at baseline



Summary of primary endpoint events

	OPSUMIT 10 mg (n=242) n (%)	Placebo (n=250) n (%)
Patients with a primary endpoint event [†]	76 (31.4)	116 (46.4)
Component as first event		
Worsening PAH	59 (24.4)	93 (37.2)
Death	16 (6.6)	17 (6.8)
IV/SC prostanoid	1 (0.4)	6 (2.4)

The beneficial effect of OPSUMIT was primarily attributable to a reduction in clinical worsening events (decreased 6MWD, worsened PAH symptoms, and need for additional PAH treatment).¹

[†]No patients experienced an event of lung transplantation or atrial septostomy in the placebo or OPSUMIT 10 mg treatment groups.

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.

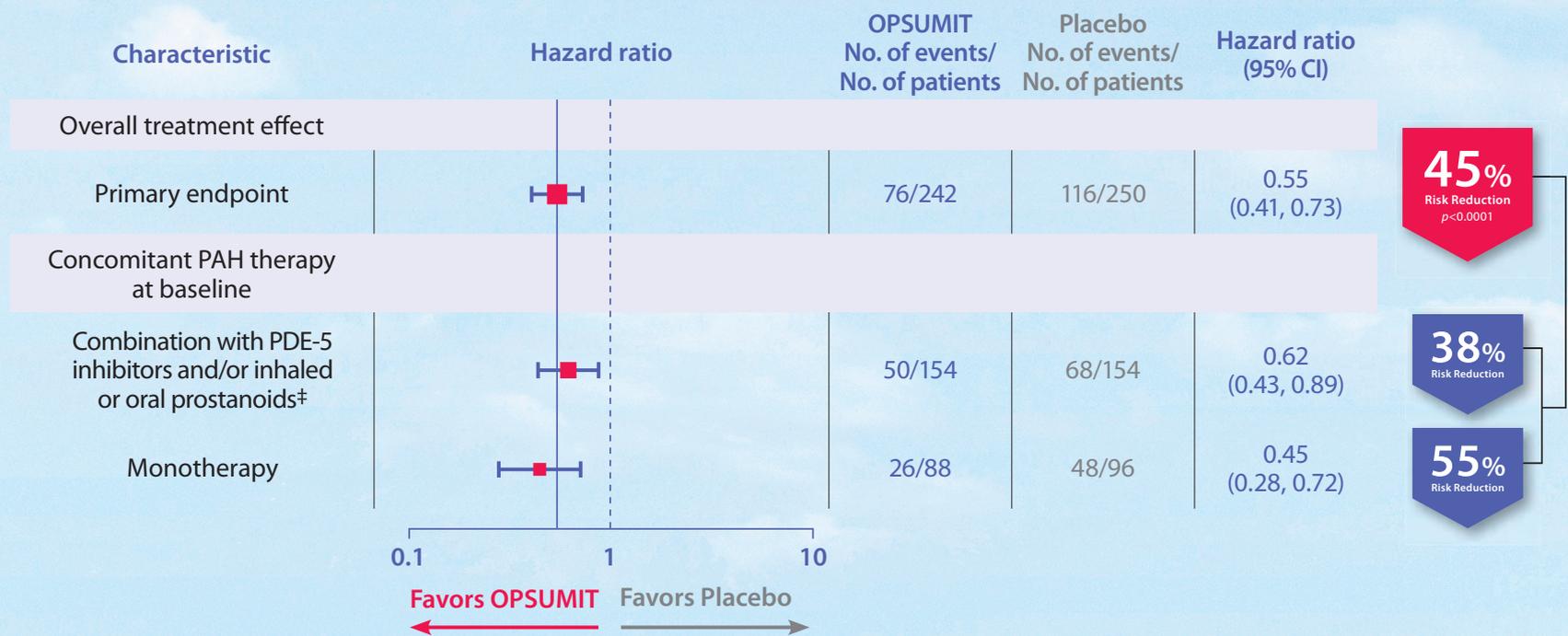
Please see Important Safety Information throughout and Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.

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%).

OPSUMIT provided consistent efficacy on the primary endpoint as monotherapy or in combination with PDE-5 inhibitors or inhaled prostanoids¹

Subgroup analysis of the primary endpoint in the SERAPHIN study



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 prostanoids¹

ADVERSE REACTIONS

- Most common adverse reactions (more frequent than placebo by $\geq 3\%$) 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: 1. OPSUMIT full prescribing information. Actelion Pharmaceuticals US, Inc. February 2015. 2. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809-818. 3. Center for Drug Evaluation and Research, Food and Drug Administration. Opsumit (macitentan) NDA 204410. Medical Review(s). 19 October 2013. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000MedR.pdf. Accessed April 15, 2015.

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.



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macitentan tablets 10 mg



Rx only

BRIEF SUMMARY

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

WARNING: EMBRYO-FETAL TOXICITY

- **Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal 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 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%).

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.

OPSUMIT® (macitentan)

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

	OPSUMIT 10 mg (N=242)	Placebo (N=249)
>3 × ULN	3.4%	4.5%
>8 × ULN	2.1%	0.4%

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 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 3.6 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 2: Adverse Reactions

Adverse Reaction	OPSUMIT 10 mg (N=242)	Placebo (N=249)
Anemia	13%	3%
Nasopharyngitis/pharyngitis	20%	13%
Bronchitis	12%	6%
Headache	14%	9%
Influenza	6%	2%
Urinary tract infection	9%	6%

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 drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see *Clinical Pharmacology (Pharmacokinetics)*]. Use other PAH 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 in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

Pediatric use

The safety and efficacy of OPSUMIT in children have not been established.

Geriatric 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 (intrauterine devices (IUD), contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Males

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 (60 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.

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

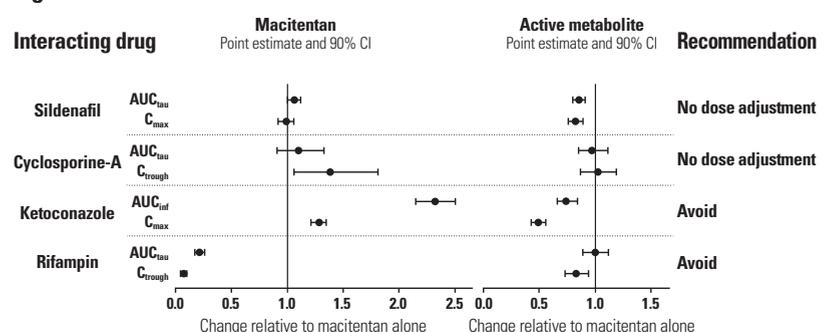
In vitro studies

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



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 vitro* and *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.
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South San Francisco, CA 94080, USA
ACT20150219

Reference: 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. February 2015.
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Reductions in mortality seen

Pediatric PH from page 1

Project of the Agency for Healthcare Research and Quality.

Of the estimated 43 million pediatric discharges that occurred between 1997 and 2012, 0.13% were for pediatric pulmonary hypertension, and discharges for the condition increased over the study period, from 1 in 1,000 in 1997 to 1 in 500 in 2012 (P less than .0001). During the same time period, inflation-adjusted national

hospital charges for pediatric pulmonary hypertension hospitalizations increased from \$926 million to \$3.12 billion (P = .0003).

The increase in discharges was most pronounced between 2006 and 2012, and most pediatric pulmonary hypertension hospitalizations did not occur in dedicated children's hospitals. The mortality of patients discharged with pulmonary hypertension was 5.9%,

and improved between 1997 and 2012 (P less than .0001).

Limitations of the study include the fact that the Kids' Inpatient Database does not provide longitudinal data on patients with PH or on outpatient care, and that ICD-9-CM codes "do not permit accurate identification of subgroups of patients with PH in a way that is consistent

with the most current schemata for categorizing PH."

Nevertheless, the study "is useful in demonstrating the burgeoning number and nature of pediatric PH hospitalizations and the implications of these trends for resource utilization and public policy."

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VITALS

Key clinical point: Pediatric pulmonary hypertension is associated with a rapidly increasing number of hospital discharges and magnitude of health care costs.

Major finding: Hospital discharges increased from 1 in 1,000 in 1997 to 1 in 500 in 2012 (P less than .0001).

Data source: A retrospective analysis of pediatric PH hospitalizations in the Kids' Inpatient Database between 1997 and 2012.

Disclosures: The researchers reported having no relevant financial disclosures.

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Dr. Vera A. De Palo, MBA, FCCP, is Medical Editor in Chief of CHEST Physician.

VIEW ON THE NEWS

Likely 'the tip of the iceberg' on this issue

It is likely that data from this report represent "the tip of the iceberg" regarding the true impact of pediatric pulmonary hypertension on hospitalizations, resource utilization, costs, and clinical outcomes.

The actual health care costs and resource needs of pediatric pulmonary hypertension, as with other chronic diseases, are limited by a lack of data linking inpatient with outpatient care, in which frequent clinic appointments and diagnostic evaluations are essential for improving outcomes well beyond inpatient care alone.

The impact of pediatric pulmonary hypertension also may be underestimated in these data because the diagnosis and its evaluation are complex, and the role of PH may not be recognized in some clinical settings by health care providers.

Despite growing recognition and awareness of PH in many settings, such as prematurity, Down syndrome, obstructive sleep apnea,

sickle cell disease, oncologic disorders, chronic lung diseases, liver disease, and others, PH is often a "hidden" contributor to morbidities and outcomes.

More research is needed to best define an optimal PH center for children, but it is likely that this goal will require creation of interdisciplinary teams of cardiologists, pulmonologists, intensivists, neonatologists, and other subspecialists, along with approaches that enhance collaboration between centers.

Dr. Steven H. Abman and Dr. D. Dunbar Ivy are with the pediatric heart lung center in the department of pediatrics at the University of Colorado at Denver Anschutz Medical Center and Children's Hospital Colorado, Aurora. These remarks were excerpted from a commentary that appeared online in *Pediatrics* on July 6, 2015 (doi/10.1542/peds.2015-1697). The authors reported having no relevant financial disclosures.

CHEST Physician

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Viral causes

CAP etiology from page 1

coccus pneumoniae in 5%, which was the most commonly detected bacterium (N. Engl. J. Med. 14 July 2015 [doi:10.1056/NEJMoa1500245]).

CAP is thought to be caused most often by *S. pneumoniae* and other bacteria; the fact that viruses were more frequently detected “probably reflects the direct and indirect benefit of bacterial vaccines,” but also “relatively insensitive diagnostic tests,” said the investigators, led by CDC medical epidemiologist Dr. Seema Jain.

The project, dubbed the Etiology of Pneumonia in the Community (EPIC) study, “adds to the growing evidence of the contribution of viruses to hospitalizations of adults.”

It also suggests “that improving the coverage and effectiveness of recommended influenza and pneumococcal vaccines and developing effective vaccines and treatments for human metapneumovirus, respiratory syncytial virus, and parainfluenza virus” – also found in study patients – “could reduce the burden of pneumonia among adults,” the researchers said.

The work matters because “the last U.S. population-based incidence estimates of hospitalization due to community-acquired pneumonia were made in the 1990s, before the availability of the pneumococcal conjugate vaccine and more sensitive molecular and antigen-based laboratory diagnostic tests. Thus, contemporary population-based etiologic studies involving U.S. adults with pneumonia are needed,” they noted.

Blood, urine, and respiratory cultures; serologic testing; antigen detection; molecular diagnostics, and

chest x-rays were all used to find the cause of disease.

The fact that infections were found in just 38% of the patients could have something to do with the team’s “inability to obtain lower respiratory tract specimens, antibiotic use before specimen collection, [and] insensitive diagnostic

tests for known pathogens,” among other problems, the researchers said.

There was a low prevalence of *Enterobacteriaceae* (1%) and other gram-negative bacteria, probably because patients with recent hospitalizations and severe immunosuppression were excluded. Subjects

were on average 60 years old.

The CDC’s National Center for Immunizations and Respiratory Diseases funded the work. Several of the authors disclosed ties to industry, including GlaxoSmithKline, Abbvie, and Pfizer.

aotto@frontlinemedcom.com

10 years ago, Boehringer Ingelheim made history in COPD treatment,



but that was only the beginning...

VIEW ON THE NEWS

Dr. Vera A. De Palo, MBA, FCCP, comments: This multi-center CDC study investigating the etiology of community-acquired pneumonia (CAP) in hospitalized patients confirms the long-held belief that a pathogen is recovered in only a minority of the cases of CAP. The results highlight the varied nature of the identified pathogens and the predominance of viral pathogens. The authors suggest that improving the coverage and effectiveness of vaccines could help reduce the burden of pneumonia in adults.

Drug will ‘maintain lung function’

CF drug from page 1

patients with the G551D mutation (about 4% of patients with CF), and its indications have been expanded since that time to include other CFTR gene mutations.

Dr. Robert Giusti, FCCP, director of the pediatric cystic fibrosis center at New York University Langone Medical Center, said in an interview that although new treatments have

improved survival and patients with CF are now living longer, “we haven’t been able to reverse the downward trend in pulmonary function,” which is about 1%-2% a year in patients with CF.

For a significant number of patients with CF, treatment with Orkambi “will reverse that trend and

will allow them to maintain their lung function,” he added.

Referring to the discovery of the CF gene in 1989, he pointed out that the availability of this treatment for half of all patients with CF is the culmination of more than 25 years of research.

The approval is “very, very excit-



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

Contains tiotropium, the active ingredient in



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.

ing,” said Dr. Susan Millard, FCCP, director for clinical research for the pediatric cystic fibrosis care center at Helen DeVos Children’s Hospital, Grand Rapids, Mich.

Ivacaftor alone was not effective in patients with two copies of the F08del mutation, and both drugs are needed for the beneficial effects, she

Ivacaftor alone was not effective in patients with two copies of the F08del mutation, and both drugs are needed.

said in an interview.

Lumacaftor “is designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of

the F508del CFTR protein, and ivacaftor... is designed to enhance the function of the CFTR protein once it reaches the cell surface,” according to a statement from Vertex.

According to the prescribing information for ivacaftor/lumacaftor, “if the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.”

The indications and usage section
Continued on following page

Introducing STIOLTO™ RESPIMAT®: from the makers of SPIRIVA®

- Significant improvement in lung function* vs SPIRIVA® RESPIMAT® and olodaterol¹
- Lung function improvement starting within 5 minutes and lasting 24 hours¹
 - STIOLTO RESPIMAT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- Improved lung function vs SPIRIVA RESPIMAT earlier in the course of COPD²
- Reduced rescue medication use at week 52¹
- Frequency of adverse events in patients taking STIOLTO RESPIMAT was comparable to that for patients taking the individual components¹

Help your patients improve lung function from the start of COPD maintenance therapy with STIOLTO RESPIMAT

*FEV₁, forced expiratory volume in 1 second.

IMPORTANT SAFETY INFORMATION (CONT'D)

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 (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema).

Use with caution in patients with urinary retention, which can be associated with symptoms like difficulty passing urine and painful urination in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment (creatinine clearance of ≤ 60 mL/min) treated with STIOLTO should be monitored closely for anticholinergic side effects. Be alert to hypokalemia, which has the potential to produce adverse cardiovascular effects. Be alert to hyperglycemia.

ADVERSE REACTIONS

The most common adverse reactions with STIOLTO (>3% incidence and higher than any of the comparators tiotropium and/or olodaterol) were: nasopharyngitis, 12.4% (11.7%/12.6%), cough, 3.9% (4.4%/3.0%), and back pain, 3.6% (1.8%/3.4%).

DRUG INTERACTIONS

- Use caution if administering adrenergic drugs because sympathetic effects of olodaterol may be potentiated.
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol.
- Beta agonists, such as olodaterol, can acutely worsen the ECG changes and/or hypokalemia that may result from administration of non-potassium sparing diuretics. The action of adrenergic agents on the cardiovascular system may be potentiated by monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to

prolong the QTc interval. Therefore beta-agonists should be used with extreme caution in patients being treated with these drugs. Drugs that prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.

- Beta-blockers should be used with caution as they can inhibit the therapeutic effect of beta agonists which may produce severe bronchospasms in patients with COPD. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardio selective beta-blockers could be considered, although they should be administered with caution.
- Avoid co-administration of STIOLTO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

STIOLTO is for oral inhalation only. The STIOLTO cartridge is only intended for use with the STIOLTO RESPIMAT inhaler. Inform patients not to spray STIOLTO into the eyes.



References: 1. STIOLTO RESPIMAT Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

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

STIOLTO™
RESPIMAT®
(tiotropium bromide & olodaterol)
INHALATION SPRAY

Continued from previous page

also states that efficacy and safety “have not been established in patients with CF other than those homozygous for the F508del mutation.”

Approval was based on two double-blind, placebo-controlled studies

of 1,108 patients with CF with the F508del mutation aged 12 years and older.

In the studies, improvements in lung function among those treated with the combination drug were greater than those on placebo.

At 24 weeks, the absolute change in percent-predicted forced expira-



BMI improves, possibly because the drug results in more appropriate bicarbonate secretion.

DR. MILLARD

tory volume in 1 second (ppFEV₁) over placebo, the primary efficacy endpoint, was a mean of 2.6% and 3.0% among those treated with the 400 mg/250 mg fixed dose (two pills) every 12 hours, which were statistically significant changes. In an extension study, the effect was sustained through 48 weeks.

STIOLTO™ RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray, for oral inhalation use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing 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 [see Contraindications, Warnings and Precautions].

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STIOLTO RESPIMAT is a combination of tiotropium and olodaterol indicated for 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 RESPIMAT is not indicated to treat acute deteriorations of COPD [see Warnings and Precautions]; STIOLTO RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STIOLTO RESPIMAT in asthma have not been established.

CONTRAINDICATIONS: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication [see Warnings and Precautions]. STIOLTO RESPIMAT is not indicated for the treatment of asthma. STIOLTO RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product [see Warnings and Precautions]. 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 RESPIMAT.

WARNINGS AND PRECAUTIONS: Asthma-Related Death [See Boxed Warning]: Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists. A 28-week, placebo-controlled US study comparing the safety of another long-acting beta₂-adrenergic agonist (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta₂-adrenergic agonists, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STIOLTO RESPIMAT has been conducted. 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. [See Contraindications]. **Deterioration of Disease and Acute Episodes:** STIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STIOLTO RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STIOLTO RESPIMAT in this setting is inappropriate. STIOLTO RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STIOLTO RESPIMAT has not been studied in the relief

of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist. When beginning STIOLTO RESPIMAT, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing STIOLTO RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If STIOLTO RESPIMAT no longer controls symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of 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 dosage of STIOLTO RESPIMAT beyond the recommended dose is not appropriate in this situation. **Excessive Use of STIOLTO RESPIMAT and Use With Other Long-Acting Beta₂-Agonists:** As with other inhaled drugs containing beta₂-adrenergic agents, STIOLTO RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO RESPIMAT. If such a reaction occurs, therapy with STIOLTO RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO RESPIMAT. **Paradoxical Bronchospasm:** As with other inhaled medicines, STIOLTO RESPIMAT may cause paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STIOLTO RESPIMAT should be stopped immediately and alternative therapy instituted. **Cardiovascular Effects:** Olodaterol, like other beta₂-agonists, 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 RESPIMAT may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Long acting beta₂-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension. **Coexisting Conditions:** Olodaterol, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. **Worsening of Narrow-Angle Glaucoma:** STIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** STIOLTO RESPIMAT should be used

with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** Because tiotropium is a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects [see Use in Specific Populations]. **Hypokalemia and Hyperglycemia:** Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment [see Drug Interactions], which may increase the susceptibility for cardiac arrhythmias. Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of olodaterol with the rates similar to those for placebo controls. Olodaterol has not been investigated in patients whose diabetes mellitus is not well controlled.

ADVERSE REACTIONS: LABA, such as olodaterol, one of the active components in STIOLTO RESPIMAT, increase the risk of asthma-related death. STIOLTO RESPIMAT is not indicated for the treatment of asthma [see Boxed Warning and Warning and Precautions]. The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions [see Warnings and Precautions]; Paradoxical bronchospasm [see Warnings and Precautions]; Worsening of narrow-angle glaucoma [see Warnings and Precautions]; Worsening of urinary retention [see Warnings and Precautions]. **Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:** Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. The clinical program for STIOLTO RESPIMAT included 7151 subjects with COPD in two 52-week active-controlled trials, one 12-week placebo-controlled trial, three 6-week placebo-controlled crossover trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1 dose of STIOLTO RESPIMAT. Adverse reactions observed in the ≤12-week trials were consistent with those observed in the 52-week trials, which formed the primary safety database. The primary safety database consisted of pooled data from the two 52-week double-blind, active-controlled, parallel group confirmatory clinical trials. These trials included 5162 adult COPD patients (72.9% males and 27.1% females) 40 years of age and older. Of these patients, 1029 were treated with STIOLTO RESPIMAT once daily. The STIOLTO RESPIMAT group was composed of mostly Caucasians (71.1%) with a mean age of 63.8 years and a mean percent predicted FEV₁ at baseline of 43.2%. In these two trials, tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used. In these two clinical trials, 74% of patients exposed to STIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 5 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for STIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 5 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation and pneumonia. Table 1 shows all adverse drug reactions that occurred with an incidence of >3% in the STIOLTO RESPIMAT treatment group and a higher incidence rate than the active comparator groups listed.

There also were reductions in pulmonary exacerbations, improvements in body mass index, and Cystic Fibrosis Questionnaire-Revised improvements – secondary endpoints that favored the treatment arms, according to company presentations at the FDA panel meeting where the drug was reviewed in May.

One of the issues raised by FDA advisers then was that there was no substantial evidence that the efficacy of the combination was greater than with ivacaftor alone.

But despite the lack of monotherapy arms and the inability to determine the contribution of the individual components to the treat-

ment effects, the panel agreed that the drug combination had been shown to be efficacious and voted 12-1 that the available safety and efficacy data supported approval for the proposed indication.

Dr. Millard said that one theory that may explain why BMI improves with treatment is that reduced bi-

carbonate production in CF patients increases the degradation of the pancreatic enzymes they take, and that the drug may result in more appropriate bicarbonate secretion.

This possibility is being evaluated in studies comparing bicarbonate secretion in patients on and off the drug, she said.

The drug was reviewed under the FDA's priority review program, which evaluates a drug "that may offer significant improvement in safety or effectiveness in treatment over available therapy in a serious disease or condition" in 6 months, instead of the usual 10 months, the FDA statement said.

Orkambi also has been designated as an orphan drug, because it is used to treat a rare disease.

The wholesale acquisition cost of

The wholesale acquisition cost of Orkambi is \$259,000 per year.

Orkambi is \$259,000 per year.

Vertex will offer a co-pay assistance program for patients with commercial insurance, and a free medicine program for uninsured patients who qualify, the company announced during a telephone briefing after the approval announcement.

There are an estimated 8,500 patients aged 12 and older with CF with 2 copies of the F508del mutation in the United States; about 35%-40% are on Medicaid, and the majority of the remainder have commercial insurance, according to the company.

Dr. Giusti had no disclosures. Dr. Millard, who is the local principal investigator of several Orkambi trials at her CF center, had no other relevant disclosures.

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Table 1: Number and frequency of adverse drug reactions greater than 3% (and higher than any of the comparators tiotropium and/or olodaterol) in COPD patients exposed to STIOLTO RESPIMAT: Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older

Treatment	STIOLTO RESPIMAT (once daily)	Tiotropium (5 mcg once daily)	Olodaterol (5 mcg once daily)
Body system (adverse drug reaction)	n=1029 n (%)	n=1033 n (%)	n=1038 n (%)
Infections and infestations			
Nasopharyngitis	128 (12.4)	121 (11.7)	131 (12.6)
Respiratory, thoracic, and mediastinal disorders			
Cough	40 (3.9)	45 (4.4)	31 (3.0)
Musculoskeletal and connective tissue disorders			
Back Pain	37 (3.6)	19 (1.8)	35 (3.4)

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in $\leq 3\%$ of patients in clinical studies are listed below: *Metabolism and nutrition disorders*: dehydration; *Nervous system disorders*: dizziness, insomnia; *Eye disorders*: glaucoma, intraocular pressure increased, vision blurred; *Cardiac/vascular disorders*: atrial fibrillation, palpitations, supraventricular tachycardia, tachycardia, hypertension; *Respiratory, thoracic, and mediastinal disorders*: epistaxis, pharyngitis, dysphonia, bronchospasm, laryngitis, sinusitis; *Gastrointestinal disorders*: dry mouth, constipation, oropharyngeal candidiasis, dysphagia, gastroesophageal reflux disease, gingivitis, glossitis, stomatitis, intestinal obstruction including ileus paralytic; *Skin and subcutaneous disorders*: rash, pruritus, angioneurotic edema, urticaria, skin infection, and skin ulcer, dry skin, hypersensitivity (including immediate reactions); *Musculoskeletal and connective tissue disorders*: arthralgia, joint swelling; *Renal and urinary disorders*: urinary retention, dysuria, and urinary tract infection.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of olodaterol, one component of STIOLTO RESPIMAT may be potentiated [see *Warnings and Precautions*]. **Sympathomimetics, Xanthine Derivatives, Steroids, or Diuretics:** Tiotropium has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids, without increases in adverse reactions. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol [see *Warnings and Precautions*]. **Non-Potassium Sparing Diuretics:** The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of STIOLTO RESPIMAT with non-potassium sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs:** STIOLTO RESPIMAT, as with other drugs containing beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and the olodaterol

component of STIOLTO RESPIMAT may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g. as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid co-administration of STIOLTO RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions and Adverse Reactions*]. **Inhibitors of Cytochrome P450 and P-gp Efflux Transporter:** In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of olodaterol maximum plasma concentrations and AUC was observed [see *Pharmacokinetics*]. Olodaterol was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment of STIOLTO RESPIMAT is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies with STIOLTO RESPIMAT or its individual components, tiotropium bromide and olodaterol, in pregnant women. Animal reproduction studies were conducted with the individual components of STIOLTO RESPIMAT, tiotropium bromide and olodaterol. STIOLTO RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Tiotropium:** No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the recommended human daily inhalation dose (RHDID; on a mcg/m² basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at approximately 40 times the RHDID (on a mcg/m² basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at approximately 430 times the RHDID (on a mcg/m² basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the RHDID (on a mcg/m² basis at maternal inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). **Olodaterol:** Olodaterol was not teratogenic in rats at approximately 2731 times the RHDID (on an AUC basis at a maternal inhalation dose of 1054 mcg/kg/day). Placental transfer of olodaterol was observed in pregnant rats. Olodaterol has been shown to be teratogenic in New Zealand rabbits at approximately 7130 times the RHDID in adults (on an AUC basis at a maternal inhalation dose of 2489 mcg/kg/day). Olodaterol exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at approximately 1353 times the RHDID in adults (on an AUC basis at a maternal inhalation dose of 974 mcg/kg/day). **Labor and Delivery:** There are no adequate and well-controlled human studies that have investigated the effects of STIOLTO RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STIOLTO RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. **Nursing Mothers:** Clinical data from nursing women or infants exposed to STIOLTO RESPIMAT or its individual active components are not available. Tiotropium, olodaterol, and metabolites of olodaterol are excreted into the milk of lactating rats. It is not known whether these compounds are excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if STIOLTO RESPIMAT is administered to a nursing woman. **Pediatric Use:** COPD does not normally occur in children. The safety and effec-

tiveness of STIOLTO RESPIMAT in the pediatric population has not been established. **Geriatric Use:** Based on available data, no adjustment of STIOLTO RESPIMAT dosage in geriatric patients is warranted. Of the 1029 patients who received STIOLTO RESPIMAT at the recommended dose once daily in the clinical studies from the pooled 1-year database, 525 (51.0%) were < 65 years of age, 407 (39.6%) were 65 to < 75 , 96 (9.3%) were 75 to < 85 , and 1 (0.1%) was ≥ 85 . No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall. **Hepatic Impairment:** No dose adjustment is needed in patients with mild and moderate hepatic impairment. A study in subjects with severe hepatic impairment was not performed. **Renal Impairment:** No dose adjustment is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of ≤ 60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects [see *Warnings and Precautions*].

OVERDOSAGE: STIOLTO RESPIMAT contains both tiotropium bromide and olodaterol; therefore, the risks associated with overdosage for the individual components described below apply to STIOLTO RESPIMAT. **Tiotropium:** High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, were observed following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. **Olodaterol:** The expected signs and symptoms with overdosage of olodaterol are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of olodaterol. Treatment of overdosage consists of discontinuation of STIOLTO RESPIMAT together with institution of appropriate symptomatic and supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of STIOLTO RESPIMAT. Cardiac monitoring is recommended in cases of overdosage.

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Readmission costs for sepsis dwarf those for MI, CHF

BY SHARON WORCESTER
Frontline Medical News

Sepsis-related hospital readmission costs for California adults were more than double those for patients with congestive heart failure (CHF) and more than triple those for patients with acute myocardial infarction (AMI) between 2009 and 2011, a retrospective cohort analysis showed.

Male gender, residence in metropolitan areas, and greater burden of comorbidities were also associated with readmission after sepsis.

The all-cause, 30-day readmission rates among 240,198 sepsis patients, 193,153 CHF patients, and 105,684 AMI patients were 20.4%, 23.6%, and

VITALS

Key clinical point: Sepsis-related hospital readmission costs in California adults were more than double those for congestive heart failure and more than triple those for acute myocardial infarction between 2009 and 2011.

Major finding: The estimated annual costs of sepsis, CHF, and AMI readmissions were \$500 million, \$229 million, and \$142 million, respectively.

Data source: A retrospective cohort study of more than 539,000 hospitalizations.

Disclosures: Dr. Chang received research support from the National Institutes of Health.

17.7%, respectively, and the estimated annual costs of those readmissions were \$500 million, \$229 million, and \$142 million, respectively, Dr. Dong W. Chang of Harbor-UCLA Medical Center, Torrance, Calif. and colleagues reported online in *Critical Care Medicine* (doi:10.1097/CCM.0000000000001159).

Patient-level factors associated with greater likelihood of 30-day readmission after sepsis included younger age (odds ratio, 1.34 for youngest vs. oldest age categories), black race (odds

ratio, 1.29 vs. white race), Native American race (odds ratio, 2.39 vs. white race), and lower income (odds ratio, 1.13 for lowest vs. highest income quartiles).

Male gender, residence in metropolitan areas, and greater burden of medical comorbidities were also associated with readmission after sepsis.

Hospital-level factors associated with greater likelihood of readmission included health care delivery to the highest vs. lowest quintile of mi-

norities (odds ratio, 1.28), for-profit status (odds ratio, 1.34), and university vs. nonuniversity hospital setting (odds ratio, 1.35), the investigators found.

The findings, which were derived from the Healthcare Cost and Utilization Project State Inpatient Database that is maintained by the Agency for Healthcare Research and Quality, show that sepsis is a leading contributor to excess health care costs related to hospital readmissions.

A better understanding of the causative events leading to sepsis readmissions is needed, the investigators noted, and if studies and policies seeking to reduce hospital readmissions are to be effective, they will need to focus on the problem of sepsis-related readmissions – on a level that is at least comparable to CHF and AMI.

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Prolonged extracorporeal lung support is predicted



M. ALEXANDER OTTO/FRONTLINE MEDICAL NEWS

BY M. ALEXANDER OTTO
Frontline Medical News

SEATTLE – Extracorporeal lung support (ELS) has evolved to the point where it can keep people alive for months as they await lung transplants. There's also an emerging role for ELS after transplant.

The technology, however, is not for everyone, according to draft guidelines from the American Association for Thoracic Surgery.

The guidelines cover dozens of ins and outs about

ELS, including how to pick the right patients and how to best perform the procedure.

The technology is ever improving, so it's possible to imagine ELS being used for years at some point, instead of months, guideline co-author Dr. Shaf Keshavjee, a thoracic surgeon at the University of Toronto, explained in a video interview at the annual meeting of the American Association for Thoracic Surgery.

To watch the video interview, search for "Keshavjee" at www.chestphysician.org.

Extended warfarin delays return of unprovoked PE

BY MARY ANN MOON
Frontline Medical News

Adding an extra 18 months of warfarin therapy to the standard 6 months of anticoagulation delays the recurrence of venous thrombosis in patients who have a first episode of unprovoked pulmonary embolism – but the risk of recurrence resumes as soon as the warfarin is discontinued, according to a report published online July 7 in *JAMA*.

"Our results suggest that patients such as those who participated in our study require long-term secondary prophylaxis measures. Whether these should include systematic treatment with vitamin K antagonists, new anticoagulants, or aspirin, or be tailored according to patient risk factors (including elevated D-dimer levels) needs further investigation," said Dr. Francis Couturaud of the department of internal medicine and chest diseases, University of Brest (France) Hospital, and his associates (*JAMA* 2015;314:31-40).

Adults with a first episode of unprovoked VT are at much greater risk of recurrence when the standard 6 months of anticoagulation runs out, compared with those whose VT is provoked by a known, transient risk factor such as lengthy surgery, trauma with immobiliza-

tion of the lower limbs, or bed rest extending longer than 72 hours.

Some experts have advocated extending anticoagulation further in such patients; but whether this is actually beneficial remains uncertain, the investigators said, because most studies have not pursued follow-up beyond the end of treatment.

The researchers performed a multicenter, double-blind trial in which 371 consecutive patients with a first episode of unprovoked PE completed 6 months of anticoagulation and then were randomly assigned to a further 18 months on either warfarin or matching placebo.

During this 18-month treatment period, the primary outcome – a composite of recurrent VT (including PE) and major bleeding – occurred in 3.3% of the warfarin group and 13.5% of the placebo group.

That significant difference translated to a 78% reduction in favor of warfarin (hazard ratio, 0.22), Dr. Couturaud and his associates said.

However, after the treatment period ended, the composite outcome occurred in 17.7% of the warfarin group and 10.3% of the placebo group. Thus, the risk of recurrence returned to its normal high level once warfarin was discontinued, the study authors noted.

CRITICAL CARE COMMENTARY: PAH in the ICU: Time for excellence

BY DR. TAMMY WICHMAN,
FCCP

Severe septic shock despite volume resuscitation on three vasopressors: the ICU team can handle it, putting in lines and ordering antibiotics. Massive GI bleed needing prothrombin complex, packed red blood cells, and urgent endoscopy: the ICU team is there, protecting the airway and optimizing tissue perfusion. Acute ST-elevation myocardial infarction postpercutaneous coronary intervention in hypoxic respiratory failure from cardiogenic edema: the ICU team is on top of it, managing the ventilator and optimizing hemodynamics.

However, admit a patient with severe pulmonary arterial hypertension (PAH) receiving continuous prostanoïd infusion, and the ICU team is no longer a well-oiled machine.

Pulmonary hypertension management in critically ill patients is challenging and, unfortunately, there are few randomized controlled trials to provide evidence-based management of critically ill patients with comorbid severe pulmonary hypertension. Current PAH guidelines do not specifically address ICU management of patients with pulmonary hypertension, but here are some recommendations to optimize care based on expert opinion:

1. Identify the right resources. You need to know your nearest pulmonary hypertension specialists and refer judiciously.

High-volume, specialized pulmonary hypertension centers have been shown to obtain the best outcomes for patients while maintaining patient satisfaction, lowering complication rates, shortening length of hospital stay, and providing the best value to health-care payers (Galie et al. *JACC*. 2013;62[25];suppl D60). The most recent pulmonary hypertension guidelines from Nice recommend referral for all patients with PAH. However, it is even more important for critically ill patients with PAH to be managed by the experts.

2. Know the right ventricle. Just like the pediatricians tell the internists that children are not “little adults,” we know the right ventricle is not a “little left ventricle.”

The right ventricle is morphologically and embryologically distinct from the left ventricle and, thus, contracts differently. The normal right ventricle utilizes coronary perfusion throughout the cardiac cycle. The

right ventricular cycle is, however, closely interrelated to the left ventricle due to the shared interventricular septum.

3. Monitor closely. Evaluation of cardiac function is critical. Echocardiography and pulmonary artery catheterization are important – at least until we get randomized controlled trials that show they are not beneficial in this patient population (Hooper et al. *Am J Respir Crit Care Med*. 2011;184[10]:1114). In a retrospective review of 99 patients admitted to UCLA ICUs with PAH, pulmonary artery catheter placement was associated with improved 6-month mortality but not ICU mortality (Huynh et al. *J Crit Care*. 2012;27:e7). It is also key to assess end organ function, including measurement of troponin, natriuretic peptides, lactate levels, and assessment of renal, hepatic, and neurologic function. Acute kidney injury is associated with increased risk of death (Haddad et al. *J Card Fail*. 2011;17[7]:533).

4. Look for triggers of right ventricle failure. Among others, these include sepsis, arrhythmias, pericardial effusion, anemia, hypoxemia, acidosis, metabolic abnormalities, withdrawal of pulmonary vasodilators, pulmonary embolism, and myocardial infarction. A French series of 46 patients with PAH admitted to the ICU for right ventricle failure found a causative factor in 41% of patients (Sztrymf et al. *Eur Respir J*. 2010;35[6]:1286).

5. Volume management is complex. Too much fluid and too little fluid can be detrimental.

6. Maintain cardiac output and systemic blood pressure. The beta₁-agonist dobutamine augments myocardial contractility and decreases afterload. However, patients with PAH may not be able to handle the associated tachycardia or the decrease in systemic vascular resistance. With profound hypotension, the alpha- and beta-receptor agonist norepinephrine is likely the best option, but it may increase pulmonary vascular resistance. Vasopressin may be used – it does cause systemic vasoconstriction and pulmonary vasodilation – but its use is limited to case reports (Tayama et al. *Interact Cardiovasc Thorac Surg*. 2007;6[6]:715).

7. Oxygenation is critically important. Maintaining adequate oxygenation prevents any contributing hypoxic vasoconstriction. Endotracheal intubation of patients with pulmonary hypertension and right ventricle failure should be avoided

when possible. If intubation is necessary, avoid propofol due to systemic hypotension (Poor et al. *Prog Cardiovasc Dis*. 2012; 55[2]:187). Hypercapnia should also be avoided, as it can cause pulmonary vasoconstriction.

8. Use PAH-targeted therapies to reduce right ventricle afterload appropriately. Prescription of PAH medications should be limited to those with expertise in the field. Just like the guidelines tell us for pulmonary hypertension in general, make sure you are treating a Group 1 patient before starting specific PAH therapies. It is certainly much more common to have pulmonary hypertension from left heart disease or hypoxic respiratory failure in the ICU.

Although pulmonary hypertension may complicate the acute respiratory distress syndrome (ARDS), it is not clear that treating the elevated pulmonary artery pressures makes a difference in outcomes. If patients are, indeed, Group 1 PAH, remember that IV epoprostenol remains the only PAH therapy for which improved survival has been demonstrated in a randomized controlled trial (Barst et al. *N Engl J Med*. 1996;334[5]:296).

9. Never stop the infusion of epoprostenol. However, doses may need to be reduced during critical illness, such as septic shock. Protect your infusion line: do not allow access for other medications and only nurses with experience loading the line should be caring for the patient. To this end, a multidisciplinary team that includes physicians, nurses,

pharmacists, and care coordinators is ideal.

10. Patients die of right ventricular failure. Outcomes of patients with PAH who require the ICU are quite poor, with mortality rates 32% to 41% (Sztrymf et al). Right ventricular failure is the most common cause of death in patients with pulmonary hypertension.

Whether it is someone with long-standing PAH and decompensated right ventricle failure despite maximal medical therapy or a newly diagnosed patient with suspected connective tissue disease and pericardial tamponade, patients with pulmonary hypertension are fragile and need to be handled with care – the best care possible.

With the development of pulmonary hypertension centers of excellence, isn't it time to consider pulmonary hypertension ICUs of excellence? Such a paradigm shift will increase the likelihood that patients with pulmonary hypertension are cared for by experts in the field and that clinical trials will be developed so that we can provide true evidence-based care.

Dr. Tammy Wichman, FCCP, is an Associate Professor and Chief of the Division of Pulmonary and Critical Care Medicine at Creighton University School of Medicine in Omaha, Nebraska. She is the Medical Director of the ICU at Creighton University Medical Center, as well as the Director of the Internal Medicine Residency Program at Creighton University.

EDITOR'S COMMENT

In this installment of *Critical Care Commentary*, Dr. Tammy Wichman shares her thoughts on a notoriously difficult group of patients to manage in the ICU – patients with pulmonary hypertension. When critically ill, these patients are some of the most challenged to encounter in the ICU, given their complicated physiology, their unique medications, and their generally poor outcomes. When faced with such challenging



patients and anticipated bad endpoints, clinicians generally look to evidence-based guidelines to help them optimize care. In this particular instance, critical care practitioners are hindered by an utter

void of data-driven guidance. The Nice guidelines' paucity of recommendations specific to pulmonary hypertension care in the ICU reflects the limits of primary supporting data in this realm. Dr. Wichman's observations combine personal experience and expert opinion with our limited clinical trial results. In addition to providing us a useful summary – lack of evidence aside – this commentary reminds us that while we have made great

strides in managing pulmonary hypertension in the outpatient setting, we need to do more for these patients when they require ICU care.

Dr. Lee Morrow, FCCP

PULMONARY PERSPECTIVES: PORT for non-small cell lung cancer

BY DR. JAMES BUTLER

The use of postoperative radiation therapy (PORT) for patients with resected non-small cell lung cancer has been declining over the last several decades.

This is likely primarily due to studies that show that such radiation therapy can have a detrimental effect on survival. This is best summarized in the “meta-analysis study” (*Cochrane Database Syst Rev*. 2005;(2):CD002142) that demonstrated an 1.18 increase risk of death.

However, many studies included in the meta-analysis also demonstrated that postoperative radiation therapy can improve local control.

Additionally, many radiation oncologists assert that detrimental survival can be avoided by the use of more modern radiation techniques that are now widely available, such as CT scan planning and image-guided radiation therapy. So, in this article we will define when PORT is indicated, discuss how postoperative RT is now made safe, and define a potential future role for PORT.

Positive Margins

The first and most obvious potential use for PORT is for patients who have had resection of their non-small cell lung cancer with close or positive margins.

In radiation oncology for many tumor types, including non-small cell cancer, it has been generally assumed that resection with close or positive margins will usually lead to local recurrence if no further therapy is given. Therefore, if further resection is not possible, radiation oncologists will almost always prescribe radiation; thus, it is difficult to determine the exact benefit of radiation.

An indication of radiation oncology attitudes toward such radiation is that often it is referred to as salvage radiation instead of adjuvant radiation therapy.

Two recent reviews from the national cancer database have been

published. One study (Hancock et al. *Ann Thorac Surg*. 2015;99[2]:406) demonstrated that stage I through III with an R1 resection had an inferior survival compared with patients who had complete resections. Patients who had an R1 resection had an improved 5-year survival by adding chemoradiation therapy as compared with no additional therapy. This benefit was most pronounced for stage III patients, 30% vs 12% 5-year survival.

This review was limited in that patients who received any radiation therapy over 1,000 cGy were allowed to be entered into this review, thus, not excluding patients with inadequate doses.

A subsequent review of this database (Wang et al. *J Clin Oncol*. 2015;61;1517) limited the analysis to patients with stage II and III incompletely resected non-small cell lung cancer, who had received adequate radiation dose, 5,000 to 7,400 cGy. The addition of RT in such patients improved survival (32% vs 24% 5-year survival). This study also demonstrated improved survival across all N stages.

Thus, patients who have not had complete resection of their non-small cell cancer and cannot be re-resected to negative margins should be sent for a radiation oncology consultation.

N2 Disease

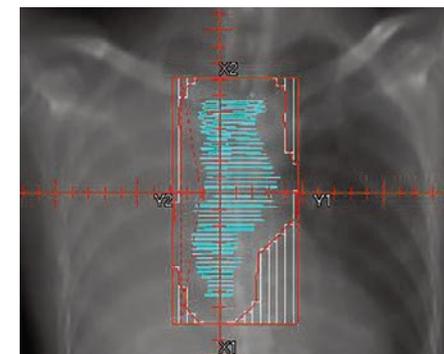
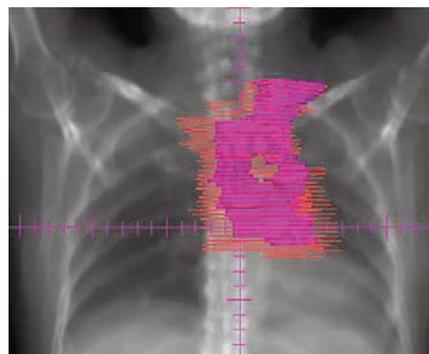
In the early days of radiation, our predecessors must have observed many recurrences even after resection of early stage non-small cell cancer as radiation therapy was tried for all patients after surgery.

As previously noted in the “meta-analysis study” (*Cochrane Database Syst Rev*. 2005 Apr 18;[2]:CD002142), such indiscriminate use of radiation therapy led to a detrimental effect on survival. However, the meta-analysis has been updated as time has gone on and now no longer shows detrimental survival for the N2 category.

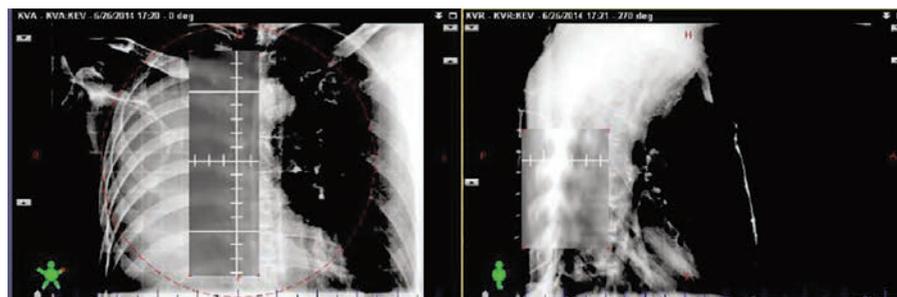
Additionally the SEER data analysis (Lally et al. *J Clin Oncol*. 2011; 24[19]:2998) of patients with stage II and III resected non-small cell lung



DR. BUTLER



Left, volumes drawn from a CT scan (3D), in pink, are smaller than volumes previously drawn from a radiograph (2D), in orange. Right, CT scans (3D planning) can enable one to avoid sensitive structures, such as the heart and lung, for the patient who had a pneumonectomy, very important if the patient only has one lung and because with only one lung, any heart damage can be even more problematic.



Images are fused on vertebra thus allowing accurate daily set up and tighter margins around target volume.



Left, Carina at expiration. Right, Carina at inspiration (moves inferiorly).

cancer demonstrated an improved survival in patients with N2 disease (27% vs 20% 5-year survival).

Also, our medical oncology colleagues have demonstrated that adjuvant chemotherapy can increase overall survival, particularly for patients with node-positive disease.

Therefore, since we know that PORT to the mediastinum can improve local control and may improve survival for node-positive mediastinal disease, it has been hypothesized that perhaps the addition of radiation to chemotherapy for such patients can

improve survival beyond what can be achieved with surgery and chemotherapy alone. This hypothesis is supported by the results from the Adjuvant Navelbine International Trialist Association (Douillard et al. *Int J Radiat Oncol Biol Phys*. 2008;72[3]:695), where in patients with stage I through stage III resected non-small cell lung cancer were randomized to receive cisplatin and vinorelbine vs observation. PORT was recommended for N+ disease but not mandatory. PORT improved survival in N2 patients (median survival

Continued on following page

Invasive approaches ‘overused’ for lung nodules

BY BIANCA NOGRADY
Frontline Medical News

FROM CHEST

One in four intermediate-sized (8-20 mm) pulmonary nodules were malig-

nant, based on a retrospective study of 377 patients in 18 community pulmonology practices. Further, despite guideline recommendations for surveillance of pulmonary nodules with less than a 5% pretest probability of

malignancy, 44% of 36 patients with low-risk pulmonary nodules underwent at least one invasive procedure, wrote Dr. Nichole T. Tanner of the Medical University of South Carolina, Charleston, and her coauthors

(*Chest* 2015 June 18 [doi:10.1378/chest.15-0630]). Noninvasive options to gauge if a nodule is malignant include CT scanning with volumetric software to measure diameter and volume-doubling time of a nodule.

Continued from previous page

improved from 12.7 to 22.7 months in the no chemotherapy arm and median survival improved from 23.8 vs 47.4 months in the chemotherapy arm).

Thus, for patients who have had resection of N2 disease with negative margins, there is a probable improved survival by adding radiation.

How do we do radiation therapy?

This is a very important question to answer since prior studies have demonstrated that radiation therapy can hurt patients.

Patients can be hurt by irradiating too much of the heart, leading to heart disease, or too much lung, leading to trouble breathing. Premature death can result.

In most of the studies included in the meta-analysis, patients had been irradiated to the entire mediastinal shadow, ipsilateral hilar shadow, and bronchial stump. Also, some patients were treated with older cobalt machines (necessary to use larger margins) and with straight lateral off cord portals (the spinal cord can only receive 45 Gy, thus mandating that some of the dose be given with portals that miss the spinal cord).

Once CT scan simulation became widely available, the nodal regions at risk within the mediastinum and ipsilateral hilum were able to be contoured, and radiation to the entire mediastinal shadow, adjacent lung, and adjacent heart have been reduced.

Every day, a patient is imaged on the radiation machine to check the position with a CT scan (cone beam CT) or orthogonal radiographs (image-guided radiation therapy). Accuracy of daily setup is enhanced, and tighter margins can be used around the target volume.

More recent technology has allowed radiation oncologists to manage respiratory motion and use IMRT to limit the volume of tissue treated to high doses outside of the target volume. In a study from MD Anderson (Liao et al. *Int J Radiat Oncol Biol Phys.* 2010;76[3]:775), this has been demonstrated to reduce toxicity for patients who receive full dose RT.

Is there a role for PORT for N1 disease?

As previously noted, PORT can reduce survival if used indiscriminately and, particularly, if larger fields are used. Because technology has improved enabling less toxicity, the possibility of giving adjuvant PORT for patients who have had surgery for N1 disease is again being considered. A multi-institutional review (Varlotto et al. *Int J Radiat Oncol Biol Phys.* 2011;81[2]:353) demonstrated

that 30% of patients experienced a local failure. Two-thirds of these local failures would have been in a standard RT portal. A more recent study from China (Fan et al. *Radiat Oncol.* 2013;8:286) demonstrated a 20% local failure rate. Patients who had positive lymph nodes at station 10 and inadequate mediastinal lymph node

dissection (less than or equal to three mediastinal nodes taken) had 35% and 30% local failure rates, respectively. This increased to almost 50% if the patient had both factors present.

Summary

PORT has a small but important role to play for patients with in-

completely resected non-small cell lung cancer, N2 disease, and, in the future, may also be added again to patients after resection of N1 disease.

Dr. Butler is with the Department of Radiation Oncology, Maimonides Cancer Center, Brooklyn, NY.

GRANTED BREAKTHROUGH THERAPY DESIGNATION FOR IPF DURING FDA REVIEW¹

SLOW THE PATH OF IPF PROGRESSION

OFEV (nintedanib) has demonstrated reproducible reductions in the annual rate of FVC decline in 3 clinical trials²

OFEV significantly reduced the risk of first acute IPF exacerbation over 52 weeks compared with placebo in 2 out of 3 clinical trials²

Learn more about OFEV inside.

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION 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 moderate or severe hepatic impairment.
- In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
- 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. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

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

FVC, forced vital capacity.

 **OFEV**[®]
(nintedanib)
capsules 150mg

Sirolimus approved for lymphangiomyomatosis

BY MIKE BOCK
Frontline Medical News

The FDA has approved Rapamune for lymphangiomyomatosis (LAM), a rare lung

disease that mainly affects women of childbearing age and is characterized by abnormal smooth muscle growth. Rapamune (sirolimus) was originally approved in 1999 to prevent organ rejection.

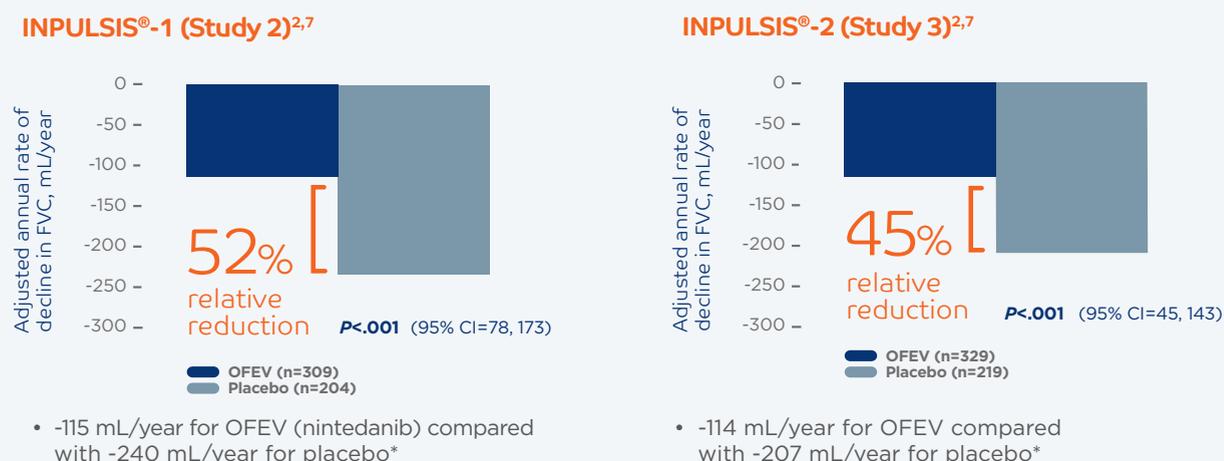
Safety and efficacy were confirmed by comparing Rapamune with placebo in 89 patients with LAM for 12 months followed by observation. The average decrease in FEV₁ was 153 mL. After halting Rapamune,

lung function declined at a rate similar to that of the placebo group. Rapamune is manufactured by Wyeth Pharmaceuticals.

mbock@frontlinemedcom.com

The totality of the evidence demonstrates that OFEV slows IPF progression²⁻⁶

REPRODUCIBLE REDUCTIONS IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 TRIALS^{2*}



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=27, 235)^{2,8}

CI, confidence interval.

*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.²

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. 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.

Cigarettes and smoking-related cancer deaths

BY RICHARD FRANKI
Frontline Medical News

Of nearly 346,000 U.S. deaths caused by smoking-related cancers in 2011, about 48% were

attributable to cigarette smoking.

Lung cancers represented 126,000 of the nearly 168,000 smoking-attributable cancers; esophageal cancers led to 7,300 deaths in 2011 based on data from five studies including the Nation-

al Health Interview Survey and the Cancer Prevention Study II, said Rebecca L. Siegel of the American Cancer Society, Atlanta, and her associates (JAMA Intern. Med. [doi:10.1001/jamainternmed.2015.2398]). Deaths

caused by smoking were down from 2001 to 2004 figures, and the prevalence of smoking fell from 23% in 2000 to 18% in 2012.

rfranki@frontlinemedcom.com

SIGNIFICANT REDUCTION IN THE RISK OF FIRST ACUTE IPF EXACERBATION OVER 52 WEEKS COMPARED WITH PLACEBO IN 2 OUT OF 3 CLINICAL TRIALS²

- **INPULSIS[®]-2** (adjudicated): HR=0.20 (95% CI=0.07, 0.56)
- **TOMORROW** (investigator-reported): HR=0.16 (95% CI=0.04, 0.71)
- **INPULSIS[®]-1** (adjudicated): HR=0.55 (95% CI=0.20, 1.54; not statistically significant)

THE MOST COMMON ADVERSE EVENTS WERE GASTROINTESTINAL IN NATURE AND GENERALLY OF MILD OR MODERATE INTENSITY²

- 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

HR, hazard ratio.



**ONE CAPSULE,
TWICE DAILY WITH FOOD²**

Not shown at actual size

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.



Proposed cause of narcolepsy link with flu vaccine

BY SHANNON AYMES
Frontline Medical News

Patients with a history of vaccination with the pandemic influenza vaccine Pandemrix

and narcolepsy were found to have antibodies to hypocretin receptor 2, possibly explaining this association after the 2009 (H1N1) pandemic.

The development of narcolepsy is associated with HLA-DQB1*0602

haplotype, loss of hypothalamic cells, and decrease production of hypocretin, a neuropeptide also known as orexin.

After the 2009 H1N1 influenza pandemic, there were increased re-

ports of narcolepsy associated with the Pandemrix vaccine in Europe. Studies of this association found a 12.7-fold increased risk of narcolepsy within 8 months of Pandemrix vaccination.

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—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. 5%), 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 (1.2% 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 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV.

Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.

Anticoagulants

- Nintedanib 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.

OFHCPISIJAN15

Please see brief summary for OFEV on the following pages.

References: 1. US Food and Drug Administration. [http://www.fda.gov/downloads/Regulatory Information/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/UCM380724.pdf](http://www.fda.gov/downloads/Regulatory%20Information/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/UCM380724.pdf). Accessed February 11, 2015. 2. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. 3. Zappala CJ et al. *Eur Respir J*. 2010;35(4):830-836. 4. Schmidt SL et al. *Chest*. 2014;145(3):579-585. 5. du Bois RM et al. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. 6. Song JW et al. *Eur Respir J*. 2011;37(2):356-363. 7. Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;370(22):2071-2082. 8. Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087.



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However, Focetria, the other H1N1 vaccine used in Europe in the 2009 pandemic, does not currently have a reported increased risk.

Likewise, studies in China indicate an increased risk of narcolepsy after infection with the 2009 pandemic H1N1 influenza virus.

“We hypothesized that differences

between the ‘adjuvanted’ A(H1N1)pdm09 vaccines Pandemrix and Focetria explain the association of narcolepsy with Pandemrix vaccinated subjects,” Dr. Syed Ahmed of Novartis Vaccines, Siena, Italy, and colleagues reported (*Sci. Transl. Med.* 2015;7:294ra105).

The researchers conducted a re-

spective analysis of sera from narcoleptic individuals vaccinated with Pandemrix and a history of H1N1 infection as well as children from Finland without a history of narcolepsy and a history of Focetria vaccination. The samples were randomized and the investigators were blinded.

By aligning protein sequences of

influenza strains, the researchers were able to identify an influenza nucleoprotein peptide similar to the hypocretin receptor.

ELISA assays detected antibodies to hypocretin receptor 2 in a significantly higher percentage of sera samples from patients with a

Continued on following page

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*]. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing 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 to not 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 continuation of 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, discontinue treatment with OFEV [see *Warnings and Precautions and Adverse Reactions*]. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 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 moderate or 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 (94%) 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. Dosage 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, 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 (nintedanib). **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 [see *Adverse Reactions*]. 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 can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryofetotoxic in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at 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 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.

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 with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for 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 bronchitis (1.2% 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. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation 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 decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain ^a	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation ^b	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension ^c	5%	4%

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

^b Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

^c Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

DRUG INTERACTIONS: P-glycoprotein (P-gp) 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-gp 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 such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust

Continued from previous page

history of Pandemrix vaccination, HLA-DQB1*0602 haplotype, and narcolepsy (17 of 20), compared with patients with a history of Focetria vaccination (0 of 6; $P < .001$) or H1N1 infection (5 of 20; $P < .001$).

Furthermore, mass spectrometry

The difference in nucleoprotein content of Focetria and Pandemrix may further explain the association of Pandemrix vaccination with narcolepsy.

indicated Focetria contained 72.7% less nucleoprotein than did Pandemrix.

ELISA assays detected fewer nucleoprotein antibodies in individuals vaccinated with Focetria than in those infected with H1N1.

Dr. Ahmed and his colleagues con-

cluded that a possible mechanism for influenza and vaccine associated narcolepsy involves nucleoprotein antigen development after vaccination or infection and cross reaction with the hypocretin receptor 2.

Furthermore, the difference in nucleoprotein content of the two vaccine types may further explain the association of Pandemrix vaccination with narcolepsy.

anticoagulation treatment as necessary [see Warnings and Precautions].

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category D. [See Warnings and Precautions]: OFEV (nintedanib) 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 apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. 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. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed

between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended [see Warnings and Precautions]. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **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.

OVERDOSAGE: In the trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Patient Information). **Liver Enzyme and Bilirubin Elevations:** Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites 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]. **Gastrointestinal Disorders:** Inform patients that gastrointestinal disorders such as diarrhea, nausea,

and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting [see Warnings and Precautions and Adverse Reactions]. **Pregnancy:** Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV [see Warnings and Precautions and Use in Specific Populations]. **Arterial Thromboembolic Events:** Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions [see Warnings and Precautions]. **Risk of Bleeding:** Bleeding events have been reported. Advise patients to report unusual bleeding [see Warnings and Precautions]. **Gastrointestinal Perforation:** Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation [see Warnings and Precautions]. **Nursing Mothers:** Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing [see Use in Specific Populations]. **Smokers:** Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. **Administration:** Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose [see Dosage and Administration].

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VIEW ON THE NEWS

Dr. David A. Schulman, FCCP, comments: For the second time, scientists have associated the European vaccination campaign against influenza that occurred after the 2009 H1N1 pan-



demic with the subsequent development of narcolepsy. The first manuscript, published in Science Translational Medicine in 2013, postulated molecular mimicry as the mechanism for which vaccinated patients developed antibodies to hypocretin; this paper was subsequently retracted due to an inability to replicate the findings. The current manuscript also suggests that mimicry may be in play, but attributes the disease to cross-reactivity to the hypocretin-2 receptor, instead of the molecule itself. While both of these theories are intriguing, in that they shine a light on the heretofore mysterious (presumed immunologic) pathophysiology of narcolepsy development, they offer little insight into the mechanism of onset for the majority of “sporadic” cases of the disease.

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Sacubitril-valsartan opens 'new chapter' for CHF

BY ELIZABETH MECHCATIE
Frontline Medical News

A combination of sacubitril, a neprilysin inhibitor, and the angiotensin receptor blocker valsartan has been approved for treating heart failure, providing what experts are describing as a major advance in the treatment of heart failure.

The approval was based on the results of the PARADIGM-HF study of about 8,400 patients with class II-IV heart failure and an ejection fraction of 40% or less. The study showed that the combination reduced the risk of cardiovascular death and hospitalization for heart failure by 20% and reduced the risk for all-cause mortality by 16%, compared with enalapril, with a favorable adverse event profile.

The approved indication for sacubitril-valsartan is to “reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure [New York Heart Association class II-IV] and reduced ejection fraction,” according to the prescribing information. The indications section includes the statement that it “is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB [angiotensin II receptor blocker].” It is contraindicated for use with ACE inhibitors, and when patients on an ACE inhibitor are switched to this drug a washout period of 36 hours before starting treatment is recommended.

Previously called LCZ696, the combination tablet formulation will be marketed by Novartis as Entresto, and will be available in three dosage strengths of sacubitril-valsartan: 24/26 mg, 49/51 mg, and 97/103 mg; in published studies of the combination, these doses are referred to as 50 mg, 100 mg, and 200 mg, respectively. The target dose is 97/103 mg twice a day.

“Many of us see this as a real sea change in heart failure management;

we’re all eager to start using this new medicine in our patients, and I think clinicians will very rapidly get a feel for this drug,” Dr. Scott D. Solomon, professor of medicine, Harvard Medical School, Boston, and one of the authors of the study, said in an interview. Referring to the trial results, he noted that for at least 10 years, there has not been a new drug for heart failure that has had this impact on



Approach this new drug with the same caution as taken with other drugs for patients with systolic heart failure.

DR. JESSUP

mortality, “so this is really quite an extraordinary finding.”

The availability of a new drug class, a neprilysin inhibitor, “opens up a new chapter in our treatment of heart failure,” said Dr. Mariell Jessup, professor of medicine at the University of Pennsylvania, Philadelphia, who was not involved in the study. “I’m very excited that we now have this new drug for use in our patients,” she said, pointing out that with the exception of ivabradine (Corlanor), approved in April, there has not been a new type of drug approved for heart failure in a long time.

Neprilysin is an endopeptidase that degrades several endogenous vasoactive peptides. Sacubitril “inhibits the breakdown of natriuretic peptides, among other vasoactive compounds, so the drug simultaneously blocks one of the neurohormonal systems that is abnormally activated in the setting of heart failure, and it also augments one of the neurohormonal systems that can be beneficial in patients with heart failure,” said Dr. Solomon, who is also director of noninvasive cardiology at Brigham and Women’s Hospital, Boston.

In PARADIGM-HF, conducted to

determine if sacubitril-valsartan was superior to treatment with an ACE inhibitor, the recognized standard treatment for heart failure, a composite of death from cardiovascular causes or a first hospitalization for heart failure (the primary outcome), was 21.8% among those randomized to the combination vs. 26.5% of those on enalapril after a median 27-month follow-up, a highly statistically significant difference that represented a 20% reduced risk over the comparator (N. Engl. J. Med. 371:993-1004). A 20% reduced risk over enalapril was seen for the two components individually in the study, which was stopped early because of the magnitude of the effect over enalapril at a dose of the ACE inhibitor that the investigators pointed out had been shown to reduce mortality, compared with placebo.

Hypotension and nonserious cases of angioedema were higher among those on sacubitril-valsartan, while renal impairment, hyperkalemia, and cough were higher in the enalapril-treated patients.

As with ACE inhibitors, there is a small risk for angioedema, and while the number of cases was low in the study, physicians need to be aware of this issue, Dr. Solomon said. “To use this effectively, patients who are on ACE inhibitors or ARBs will need to be stopped, given 36 hours to wash out, and then started on this new agent,” he said.

In an interview, Dr. Jessup said that she hopes that physicians approach this new drug with the same caution they have with other drugs for patients with systolic heart failure and encouraged clinicians to carefully read the study and familiarize themselves with the prescribing information. Patients should not be taken off an ACE inhibitor and immediately switched to Entresto, she said.

She referred to the “famous” Canadian study that identified a significant increase in spironolactone prescriptions and in the rates of hyperkalemia and hyperkalemia-associated

deaths after the positive Randomized Aldactone Evaluation Study (RALES) results were published in 1999 (N. Engl. J. Med. 2004;351:543-51). After the study, which found significant improvements in morbidity and mortality in patients with severe heart failure, was published, “physicians immediately started to put their patients on spironolactone and there was a spike in hyperkalemia and in deaths,” she noted.

The Entresto label includes a boxed warning about the risk of fetal toxicity, and the FDA statement recommends that health care professionals counsel patients about the risks to an unborn baby. One of the company’s postmarketing requirements is to conduct an epidemiologic study evaluating the incidence of angioedema in black patients treated with the combination, compared with another drug, according to the FDA’s approval letter.

The PARADIGM-HF results were reported in August 2014 at the European Society of Cardiology annual meeting in Barcelona. Dr. Solomon said that a large international study evaluating Entresto in patients with heart failure and preserved ejection fraction is currently underway.

The cost per day of Entresto is \$12.50 (the wholesale acquisition cost), and the company anticipates that the product will be available in most pharmacies within weeks of the approval date, according to a Novartis spokesperson.

Valsartan, approved in 2001, is marketed as Diovan by Novartis and is available in generic form from Ranbaxy.

The PARADIGM-HF trial was funded by Novartis. Dr. Solomon, a member of the executive committee for the study, has received research support from Novartis for the conduct of this and other studies, and has served as a consultant to the company. Dr. Jessup had no related disclosures.

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Dyslipidemia guideline predicted to draw criticism

BY MARY ANN MOON
Frontline Medical News

A new clinical practice guideline for managing dyslipidemia to reduce adults’ CVD risk will likely draw criticism for the simple reason that it calls for change, according to the co-chairs of the panel that compiled the guideline’s 26 recommendations.

Like the existing American College of Cardiology/American Heart Association guideline, this guideline issued jointly by the U.S. Department of Veterans Affairs and the U.S. Department of Defense in January 2015 calls for eliminating the use of cholesterol levels as treatment targets. But the VA/DOD guideline differs in its more conservative approach: It recommends against the routine use of extensive testing to estimate CVD risk, calls for

a more nuanced and “shared” approach to weighing the risks and benefits of statin therapy, advocates initiating such therapy at a lower dose, and recommends against routine laboratory monitoring using liver function panels and lipid testing.

These new recommendations are based on strong and recent evidence, but they challenge previous, firmly embedded beliefs and so “will

Continued on following page

Switch clopidogrel nonresponders to prasugrel

BY BRUCE JANCIN
Frontline Medical News

PARIS – Clopidogrel nonresponsiveness is a modifiable cardiovascular risk factor in patients undergoing percutaneous coronary intervention, according to the results of the third Responsiveness to Clopidogrel and Stent-Related Events (RECLOSE-3) study.

High residual platelet activity following a loading dose of clopidogrel in patients undergoing PCI was



Clopidogrel nonresponsiveness is indeed a modifiable risk factor.

DR. ANTONIUCCI

shown in the earlier RECLOSE-2 study to be a potent predictor of an increased 2-year cardiovascular event rate (JAMA 2011;306:1215-23). This left open the question of whether switching to a different antiplatelet drug would reduce that elevated 2-year risk.

The new RECLOSE-3 study shows that this clopidogrel nonresponsiveness is indeed a modifiable risk factor.

All that's necessary is to identify affected patients via a commercially

available in vitro assay, switch them to prasugrel, and their long-term cardiac outcomes become markedly better than if they stayed on clopidogrel, Dr. David Antonucci reported at the annual congress of the European Association of Percutaneous Cardiovascular Interventions.

The prospective RECLOSE-3 study included 302 consecutive patients undergoing PCI who were determined to be clopidogrel nonresponders based upon residual platelet activity of 70% or more as measured by light transmittance aggregometry.

All were switched to prasugrel and underwent repeat platelet activity measurement.

The control group consisted of 248 clopidogrel nonresponders who stayed on the antiplatelet agent in RECLOSE-2.

It was necessary to rely on historical controls for ethical reasons; based upon the RECLOSE-2 results, it's no longer appropriate to randomize clopidogrel nonresponders to continued use of clopidogrel, according to Dr. Antonucci, head of the division of cardiology at Careggi Hospital in Florence, Italy.

Mean residual platelet reactivity improved from 78% in RECLOSE-3 participants on clopidogrel to 47% on prasugrel.

All but 6% of clopidogrel nonresponders demonstrated acceptable

VITALS

Key clinical point: Switch clopidogrel nonresponders undergoing PCI to prasugrel in order to cut their 2-year cardiac mortality risk in half.

Major finding: Patients undergoing PCI who switch to prasugrel because they show high residual platelet activity after a loading dose of clopidogrel have a 2-year cardiac mortality half that of clopidogrel nonresponders who remain on the drug.

Data source: RECLOSE-3, a prospective study of 302 patients undergoing PCI who were switched to prasugrel upon being identified as clopidogrel nonresponders and a historical control group of 248 clopidogrel nonresponders who remained on the antiplatelet agent.

Disclosures: RECLOSE-3 was funded by the Italian Department of Health. The presenter reported having no financial conflicts.

suppression of platelet activity on prasugrel.

The primary study endpoint was 2-year cardiac mortality.

With a follow-up rate of 99%, the rate was 4% in clopidogrel nonresponders switched to prasugrel, significantly better than the 9.7% in controls.

Moreover, the rate of definite stent thrombosis – a key secondary endpoint – was 0.7% in the group switched to prasugrel, fourfold lower than in controls.

Probable stent thrombosis was diagnosed in 1.6% of controls and none of the prasugrel group.

All patients in the control group from RECLOSE-2 had been admitted with an acute coronary syndrome. Restricting the analysis to the 126 RECLOSE-3 participants switched to prasugrel who had an acute coronary

syndrome upon hospitalization, the 2-year cardiac death rate was 3.2%, still significantly lower than the 9.7% in controls.

In a multivariate analysis that controlled for potential confounders – including the more frequent use of drug-eluting stents and lower prevalence of a left ventricular ejection fraction of 40% or less in the RECLOSE-3 patients – switching clopidogrel nonresponders to prasugrel was associated with a highly significant 50% reduction in the risk of cardiac death at 2 years' follow-up.

The only other significant predictors were a baseline serum creatinine greater than 1.5 mg/dL and advanced age, both of which were associated with increased risk.

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Continued from previous page

undoubtedly provoke criticism," said panel co-chairs Dr. John R. Downs of South Texas Veterans Health Care System, San Antonio, and Dr. Patrick G. O'Malley of the Uniformed Services University of the Health Sciences, Bethesda, Md.

"We hope we have brought some order to the chaos of clinical guidelines by providing a rigorous, simple, transparent, and high-quality guide-

line that providers can use to efficiently care for their patients," they noted (Ann. Intern. Med. 2015 June 22 [doi:10.736/M15-0840]).

The recommendations include:

No longer using LDL or non-HDL cholesterol levels as treatment targets, because the only data to suggest that this is beneficial are both indirect and questionable.

No routine use of new genetic, serologic, physiologic, anatomical, or

psychosocial risk markers to improve CVD risk prediction. In particular, high-sensitivity C-reactive protein testing and coronary artery calcium testing add only a little information to conventional risk calculations, do not improve CVD outcomes, and are costly; the latter test also exposes patients to potentially harmful radiation.

There is no evidence that primary prevention benefits low-risk patients (those with less than a 6% 10-year risk of CVD events) and only limited evidence that it benefits intermediate-risk patients (those at 6%-12% 10-year risk), so any decision to initiate statin therapy in this patient population must be "nuanced" and must include patient input.

For secondary prevention, statins should be initiated at a moderate dose and titrated to a higher dose only when medically indicated, such as when acute coronary syndrome or recurrent CVD events develop.

Higher doses are not consistently beneficial and are associated with side effects that may lead to de-

creased adherence with therapy.

Patients no longer need to fast before lipid testing because fasting makes only a small difference in test results that is unlikely to affect risk classification or therapeutic decisions. Moreover, fasting is a burden for patients, who may avoid lipid testing altogether if they have to fast for 9-12 hours, and a burden for laboratories because of the large number of patients who present for testing early in the morning.

Routine lipid testing to monitor treatment effect is now unnecessary because lipid levels are no longer to be used as treatment targets.

Routine liver-function tests are unnecessary because evidence doesn't show this improves detection of statin-associated liver damage (except at the highest doses), and serious liver damage is extremely rare. Moreover, frequent testing is a burden for both the patient and the clinician.

The full guideline is available at www.healthquality.va.gov/guidelines/CD/lipids

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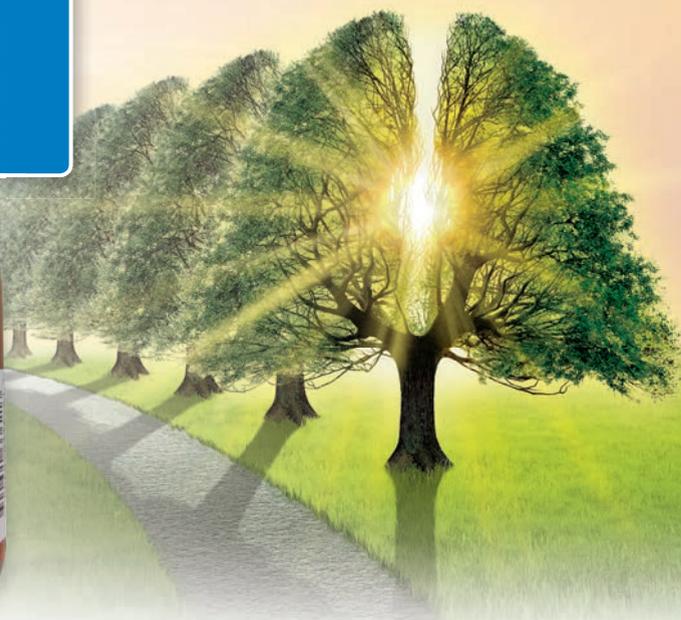
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CHEST

The screenshot shows the CHEST Physician website interface. At the top, there's a search bar and navigation tabs for HOME, CLINICAL NEWS, NEWS FROM THE ACCP, FEATURES, PRACTICE ECONOMICS, and MAIL. The main content area is titled "Featured Topic" and highlights "PULMONARY MEDICINE" with a sub-headline: "Radiological guidance does not improve intracranial stent location." Below this, there are several smaller article teasers with images and headlines, such as "High schoolers smoking more cigars, pipes, e-cigarettes" and "Biologics inch ahead in asthma treatment". A "Features" section is also visible, listing "Point/Counterpoint: Will Choosing Wisely in care?" and "Campaign pushes doctors to be the best 'YES!' Of all the tools out there -- and now the mouse -- is among the most powerful. In a system that rewards g...". At the bottom, there's a "Connect with the ACCP" link.

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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.

Consider REVATIO oral suspension for your appropriate PAH patients.
To learn more about REVATIO, please visit REVATIOHCP.com.

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

INDICATION AND USAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Nervous system Seizure, seizure recurrence.

DRUG INTERACTIONS

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B There are no adequate and well-controlled studies of sildenafil in pregnant women. No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/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 In a randomized, double-blind, multi-center, placebo-controlled, parallel-group, dose-ranging study, 234 patients with PAH, aged 1 to 17 years, body weight greater than or equal to 8 kg, were randomized, on the basis of body weight, to three dose levels of REVATIO, or placebo, for 16 weeks of treatment. Most patients had mild to moderate symptoms at baseline: WHO Functional Class I (32%), II (51%), III (15%), or IV (0.4%). One-third of patients had primary PAH; two-thirds had secondary PAH (systemic-to-pulmonary shunt in 37%; surgical repair in 30%). Sixty-two percent of patients were female. Drug or placebo was administered three times a day.

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

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

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

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

Patients with Renal Impairment No dose adjustment is required (including severe impairment CL_{Cr} <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

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Hydrocortisone improves extreme preemies' risks

BY BRUCE JANCIN

Frontline Medical News

SAN DIEGO – Early prophylactic very-low-dose hydrocortisone improved survival free of bronchopulmonary dysplasia in extremely preterm neonates in a large French randomized trial.

The intervention also had positive results on secondary endpoints, including rates of extubation by day 10 and patent ductus arteriosus closure without resort to ligation, Dr. Olivier Baud reported at the annual meeting of the Pediatric Academic Societies.

PREMILOC, a double-blind, randomized, placebo-controlled, 21-center French study, was halted by the data safety monitoring board based upon compelling evidence of superiority after scrutinizing results in the first 521 randomized subjects.

Survival free of bronchopulmonary dysplasia (BPD) at 36 weeks' gestational age occurred in 60% of the hydrocortisone group and 51% of placebo-treated controls. The number-needed-to-treat was 11 patients, said Dr. Baud, professor of pediatrics at Robert Debré Hospital in Paris and Paris Diderot University.

The intervention involved administration of intravenous hydrocortisone sodium succinate for the first 10 postnatal days. The dose was 0.5 mg/kg/12 hours for 7 days followed by 0.5 mg/kg/24 hours for 3 days. Treatment began as soon as possible after birth and always within 24 hours. The total cumulative dose of hydrocortisone was 8.5 mg/kg. That's 15-30 times less corticosteroid than employed in earlier studies of higher-dose dexamethasone, where gastrointestinal bleeding, intestinal perforation, and other serious ad-

verse events were a major problem.

All study participants were born at 24-27 weeks' gestational age. In order to minimize the risk of treatment-related serious adverse events, especially GI perforation – patients with intrauterine growth retardation or who were on nonsteroidal anti-inflammatory agents were ineligible.

The rationale for the study, Dr. Baud explained, comes from the landmark work of Dr. Kristi L. Waterberg, professor of pediatrics at the University of New Mexico, Albuquerque, who has argued that early adrenal insufficiency in extremely small-for-gestational-age infants is linked to BPD, patent ductus arteriosus, persistent lung inflammation, and poor enteral nutrition. She introduced the concept that administration of very-low-dose corticosteroids at a dose comparable to normal endogenous steroid production could serve as a global therapy addressing these multiple health problems.

Two prior studies of low-dose hydrocortisone in extremely preterm babies were halted due to an increase in GI perforation, Dr. Baud noted, which is why the French investigators excluded neonates at increased risk for this complication.

Dr. Baud said the next stage of the PREMILOC study will be to report 2-year outcomes; a greater than 90% follow-up rate is anticipated. Also, ancillary studies will examine placental findings, the impact of pretreatment serum cortisol levels, thyroid function, and other issues. "Our goal is to identify a targeted population that could strongly benefit from prophylactic hydrocortisone."

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PREMILOC: Key outcomes

	Hydrocortisone	Placebo
BPD-free survival at 36 weeks' gestational age	60%	51.1%
BPD at 36 weeks' gestational age	21.6%	26.3%
Death before 36 weeks' gestational age	18.4%	22.6%
Extubated by day 10	59.6%	43.6%
Patent ductus arteriosus ligation	14.5%	20.7%
Weaning from all supplemental O ₂ by 36 weeks	54.5%	44.7%
BPD-free survival at 36 weeks (mother had chorioamnionitis)	64.9%	52.8%
BPD-free survival at 36 weeks (mother had no chorioamnionitis)	59.3%	50.5%

Note: Based on data for the first 521 randomized subjects from PREMILOC.

Source: Dr. Baud

CMS proposes to pay for advance care planning

BY ALICIA GALLEGOS
Frontline Medical News

Physicians are praising a new proposal by the Centers for Medicare & Medicaid Services to pay for end-of-life counseling as part of a sweeping draft of updates to its 2016 physician payment schedule.

The proposed fee schedule – the first since repeal of the Sustainable Growth Rate (SGR) formula and enactment of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) – includes modifications to reimbursement policies, changes to misvalued codes, and updates to quality performance metrics for physicians who participate in the Physician Quality Reporting System (PQRS).

As part of the proposal, two new advance care planning codes would be created to pay physicians for time discussing patient options for advance directives. The first code would cover an initial 30 minutes of the doctors' time, and the second would cover additional 30-minute blocks as necessary.

Dr. Andrew W. Gurman, president-elect of the American Medical Association, said the proposed rule affirms the need to support conversations between doctors and patients about end-of-life wishes before critical medical events occur. The AMA Current Procedural Terminology (CPT) Editorial Panel and the AMA Relative Value Update Committee (RUC) created the new CPT codes and

recommended the associated payments for calendar year 2015.

"This is a patient-centered policy intended to support a careful planning process that is assisted by a physician or other qualified health care professional," Dr. Gurman said in a statement. "This issue has been mischaracterized in the past and it is time to facilitate patient choices about advance care planning decisions."

The American College of Physicians (ACP) applauded inclusion of the advance care planning codes, calling it an important step to improve care for Medicare patients with serious illnesses.

Two new codes would pay for time spent discussing advance directives. The first code would cover an initial 30 minutes; the second would cover additional 30-minute increments.

"The nation's physicians believe that conversations among physicians, patients, and loved ones is the standard of care," ACP President Dr. Wayne J. Riley said in a statement. "The College is pleased that CMS has recognized what the medical community is doing to address the needs and requests made by patients and their loved ones."

CMS' proposal also includes updates to the PQRS, the federal program that provides incentive payments to eligible professionals and group

practices that report data on quality measures for covered services and/or participate in a qualified clinical data registry (QCDR). The proposal would establish criteria for satisfactory reporting similar to that of previous years, including the general reporting of nine measures covering three National Quality Strategy domains.

Eligible professionals and practices who do not report on PQRS standards in 2016 will see their 2018 Medicare pay cut by 2%. The proposed fee schedule also would eliminate measures that are topped out, duplicative, or are being replaced with more robust measures. If the proposal is finalized, 300 total measures in the PQRS program are slated for 2016.

The proposed fee schedule also would modify the Medicare Shared Savings Program (MSSP) by:

- Allowing participants to add or delete a measure if it no longer aligns with updated clinical practice or causes patient harm.
- Clarifying how PQRS-eligible professionals participating within an ACO can meet PQRS requirements when their ACO satisfactorily reports quality measures.
- Amending the definition of primary care services to include claims submitted by certain teaching hospitals and excluding those submitted by skilled nursing facilities.

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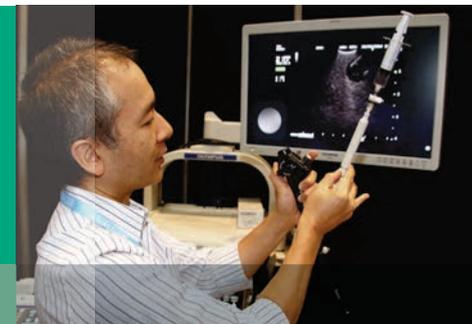
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ICD-10 COMETH: How about ICD-10 codes for COPD?

BY DR. MICHAEL E. NELSON, FCCP

There are special instructions for coding exacerbations of chronic bronchitis and asthma. The ICD-10-CM Official Guidelines for Coding and Reporting, available at www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html, specifically define an acute exacerbation of chronic obstructive bronchitis or asthma.

The codes in categories J44 and J45 distinguish between uncomplicated cases and those in acute exacerbation.

An acute exacerbation is a worsening or a decompensation of a chronic condition. An acute exacerbation is not equivalent to an infection superimposed on a chronic condition, though an exacerbation may be triggered by an infection.

You will also notice that there are “Other” codes

and “Unspecified” codes. “Other” codes are utilized when the clinical information describes a diagnosis for which a separate code does not exist. “Unspecified” codes are used when the clinical information is not sufficient to assign a more specific code.

Remember, the more specific that one is with the code, the less likely the code is to be rejected by the payer.

J40-J44 Chronic lower respiratory disease	
Excludes 1:	Bronchitis due to chemicals, gases, fumes and vapors (J68.0)
Excludes 2:	Cystic fibrosis (E84.-)
J40	Bronchitis, not specified as acute or chronic
	Bronchitis NOS Bronchitis with tracheitis NOS Catarrhal bronchitis Tracheobronchitis NOS Use additional code to identify: exposure to environmental tobacco smoke (Z77.22) exposure to tobacco smoke in the perinatal period (P96.81) history of tobacco use (Z87.891) occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-) tobacco use (Z72.0) Excludes 1: acute bronchitis (J20.-) allergic bronchitis NOS (J45.909-) asthmatic bronchitis NOS (J45.9-) bronchitis due to chemicals, gases, fumes and vapors (J68.0)
J41	Simple and mucopurulent chronic bronchitis
	Use additional code to identify: exposure to environmental tobacco smoke (Z77.22) exposure to tobacco smoke in the perinatal period (P96.81) history of tobacco use (Z87.891) occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-) tobacco use (Z72.0) Excludes 1: chronic bronchitis NOS (J42) chronic obstructive bronchitis (J44.-)
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J41.8	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
	Chronic bronchitis NOS Chronic tracheitis Chronic tracheobronchitis Use additional code to identify: exposure to environmental tobacco smoke (Z77.22) exposure to tobacco smoke in the perinatal period (P96.81) history of tobacco use (Z87.891) occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-) tobacco use (Z72.0) Excludes 1: chronic asthmatic bronchitis (J44.-) chronic bronchitis with airways obstruction (J44.-) chronic emphysematous bronchitis (J44.-) chronic obstructive pulmonary disease NOS (J44.9) simple and mucopurulent chronic bronchitis (J41.-)

J43	Emphysema
	Use additional code to identify: exposure to environmental tobacco smoke (Z77.22) history of tobacco use (Z87.891) occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-) tobacco use (Z72.0) Excludes 1: compensatory emphysema (J98.3) emphysema due to inhalation of chemicals, gases, fumes or vapors (J68.4) emphysema with chronic (obstructive) bronchitis (J44.-) emphysematous (obstructive) bronchitis (J44.-) interstitial emphysema (J98.2) mediastinal emphysema (J98.2) neonatal interstitial emphysema (P25.0) surgical (subcutaneous) emphysema (T81.82) traumatic subcutaneous emphysema (T79.7)
J43.0	Unilateral pulmonary emphysema [MacLeod's syndrome]
	Swyer-James syndrome Unilateral emphysema Unilateral hyperlucent lung Unilateral pulmonary artery functional hypoplasia Unilateral transparency of lung
J43.1	Panlobular emphysema
	Panacinar emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Emphysema, unspecified
	Bullous emphysema (lung)(pulmonary) Emphysema (lung)(pulmonary) NOS Emphysematous bleb Vesicular emphysema (lung)(pulmonary)
J44	Other chronic obstructive pulmonary disease
	Includes: asthma with chronic obstructive pulmonary disease chronic asthmatic (obstructive) bronchitis chronic bronchitis with airways obstruction chronic bronchitis with emphysema chronic emphysematous bronchitis chronic obstructive asthma chronic obstructive bronchitis chronic obstructive tracheobronchitis Code also type of asthma if applicable (J45.-) Use additional code to identify: exposure to environmental tobacco smoke (Z77.22) history of tobacco use (Z87.891) occupational exposure to environmental tobacco smoke (Z57.31) tobacco dependence (F17.-) tobacco use (Z72.0) Excludes 1: bronchiectasis (J47.-) chronic bronchitis NOS (J42) chronic simple and mucopurulent bronchitis (J41.-) chronic tracheitis (J42) chronic tracheobronchitis (J42) emphysema without chronic bronchitis (J43.-) lung diseases due to external agents (J60-J70)
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
	Use additional code to identify the infection
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
	Decompensated COPD Decompensated COPD with (acute) exacerbation Excludes 2: chronic obstructive pulmonary disease [COPD] with acute bronchitis (J44.0)
J44.9	Chronic obstructive pulmonary disease, unspecified
	Chronic obstructive airway disease NOS Chronic obstructive lung disease NOS

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 $>3\times$ 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 ($\geq 10\%$) 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.

Proven to delay progression in IPF¹

- Fewer patients had a meaningful decline in lung function with Esbriet at 52 weeks vs placebo (17% vs 32% of patients had $\geq 10\%$ decline in %FVC, $P < 0.001$). Treatment effect was evident at 13 weeks ($P < 0.001$) and increased through trial duration^{1,2,*†}
- More patients had stable lung function with Esbriet than with placebo at 52 weeks (23% vs 10%)^{2,*‡}
- In clinical trials, elevated liver enzymes, photosensitivity reactions, and gastrointestinal disorders have been reported with Esbriet²
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide³

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

*The efficacy of Esbriet was evaluated in three phase 3, randomized, double-blind, placebo-controlled trials. In ASCEND, 555 patients with IPF were randomized to receive Esbriet 2403 mg/day or placebo for 52 weeks. Eligible patients had %FVC between 50%-90% and %DL_{CO} between 30%-90%. The primary endpoint was change in %FVC from baseline to week 52.

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 (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal 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 $\geq 10\%$ decline category.

‡Stable was defined as no decline in lung function.

References: **1.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083-2092. Erratum in: *N Engl J Med.* 2014;371:1172. **2.** Esbriet full Prescribing Information. InterMune, Inc. October 2014. **3.** InterMune, Inc. Data on file.

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Rx only

BRIEF SUMMARY

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

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 $>3 \times$ 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 $\geq 3 \times$ ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations $\geq 10 \times$ 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 $\geq 3 \times$ 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*]

Clinical Trials Experience

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

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

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and 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 $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

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

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

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

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

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

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

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 CYP1A 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 CYP1A 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 an 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 old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

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

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.

OVERDOSAGE

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

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

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

INTERMUNE®

FROM THE PRESIDENT: Summer ... time to address work-life balance

BY DR. CURTIS N. SESSLER,
FCCP

There is something about the summertime that promotes appreciation for slower pace and reflection. Whether it's the cool sand between your toes, an amazing vista after a vigorous hike, or the mid-morning laughter of your kids on vacation – these joyful activities help reinvigorate. Reflecting back on 30 summers as an academic pulmonary and critical care physician, I think it may be more important than ever for us to take a moment to contemplate work-life balance in medicine, and, perhaps, our specialty in particular.

We all work hard, and most of us would enter a career in medicine again, and even sign up for the same specialty again. We value the work we do, particularly, the opportunity to improve the lives of our patients and generally find the work stimulating, rewarding, and even exciting. Additionally, we in pulmonary, critical care, and related fields, are accustomed to the stresses of high intensity, fast-pace, high-stakes work, as well as long and often undesirable work hours, including weekends and nights. There are certainly many more individuals in the hospital at night than a decade ago. Additionally, recent years have brought a rapid increase in the proportion of our time working as clinicians devoted to documentation and other non-patient care tasks. All told, the potential for work-related stress is certainly not decreasing.

A specialty at risk

Individuals who work in the ICU and similar work environments are accustomed to stress. It is part of the territory. To a point, short-term stress can actually be useful, as it tends to enhance focus and efficiency. Burnout, however, is a maladaptive response to excessive stress in the workplace and is characterized by emotional, mental, and physical exhaustion. Classically, burnout is defined as having three dimensions: emotional exhaustion, depersonalization, and diminished personal accomplishment. Importantly, development of burnout in a health-care worker has potential adverse consequences for the individual, the work environment, and our patients. Workers with burnout are more likely to have depression, alcohol and substance abuse, and various health disorders, and, often, leave the profession early. Behaviors of a burned out individ-

ual can be disruptive, contributing to staff dissatisfaction and excessive turnover. Finally, burnout has been associated with increased rates of medical errors, lower patient satisfaction, and reduced quality of care. Clearly, preventing and ameliorating burnout are important targets.

There is a growing body of evidence¹⁻⁴ that serious burnout is commonplace among ICU workers. From a broad perspective, burnout is more common, and satisfaction with work/life balance less common, among physicians compared with the general population. Not surprisingly, among both physicians and nurses, the ICU as a workplace is associated with higher-than-average rates of burnout. There are now numerous survey-based multicenter studies that indicate approximately one-third to one-half of ICU workers have severe burnout.¹⁻⁴ Look to your left. Look to your right. Chances are that one of you has significant burnout.

Particularly noteworthy is a recent online survey of physicians performed by Medscape⁴ in which 52% of intensivists described themselves as having serious burnout – the largest proportion among all 25 medical specialties reported. Perhaps more distressing, intensivists had among the lowest proportion of respondents who described themselves as “very happy” when describing their satisfaction at work and home. Finally, intensivists had the lowest propor-

The number of night shifts per month, and the time since the last nonworking week, were independent risk factors for burnout.

tion, among 25 medical specialties, of self-described health as “excellent” or “very good.”

What can be done?

We should all be concerned that these findings collectively paint a picture of a specialty at risk. It is important for us to consider why burnout occurs and what can be done about it. Specifically, which individuals are at increased risk? Are there identifiable factors that might be modified to reduce the likelihood of developing burnout? Are there individual and organizational approaches to identify individuals with burnout syndrome and mitigate its effects? Finally, are there opportunities for

key stakeholders, including administrators and policymakers, to become better informed as to this emerging epidemic?

Several studies^{1,3} have now identified independent, potentially modifiable risk factors for burnout of intensivists, as well as ICU nurses. Common themes have emerged and include the following: (a) the quality of working relationships; (b) end-of-life issues; (c) organizational factors; and (d) personal characteristics. Perhaps the most consistently noted factor is that of interpersonal conflicts, those among physicians, nurses, and patients and family members. ICU physicians and nurses with burnout more commonly described conflict with their colleagues and with the other key members



DR. SESSLER

of the ICU team. Suboptimal communication is often at the root of conflict, and there are opportunities for enhancing communications and creating a supportive and trusting environment among ICU health-care workers.

The relationships that physicians and nurses have with critically ill or injured patients, and, perhaps, more commonly with family members, can be highly stressful. Again, promoting understanding and healthy communication proactively can pay dividends in regards to stress mitigation. This ties in with the added challenges of end-of-life situations in which emotions often run high, and calm, thoughtful communication is

of critical importance. Surveys indicate^{1,3} that end-of-life issues impact our ICU nursing colleagues even more significantly, perhaps in part because of their many hours of direct contact with patients and families at the bedside.

From a unit organizational perspective, studies indicate^{1,5} that an excessively heavy work schedule is an important risk factor for physicians. In particular, the number of night shifts per month, and the time since the last nonworking week, were independent risk factors for burnout in one study. In a prospective randomized trial,⁵ a continuous intensivist schedule of 14 consecutive days was associated with higher burnout,

greater job distress, and more work-life imbalance than a schedule with weekend cross-coverage. Inclusion of nonclinical work, such as research, teaching, or administrative activities, or work in a different clinical setting, appears to be protective regarding burnout. Unit and practice leaders and administrators have an opportunity to influence scheduling and non-clinical activities to reduce burnout.

Individuals who seem to be higher risk for developing burnout tend to have perfectionist and controlling tendencies, pessimistic views, and an inability to express emotions or to delegate. Individuals with supportive relationships and those who are able to personally manage difficult situations effectively, ie, are “resilient,” tend to avoid burnout more effectively.

Strategies to manage burnout in the ICU focus on prevention, early identification of the individual with burnout, and mitigation of burnout (often employing the same techniques as for prevention). Preventive strategies include both individual and organizational approaches. Individual approaches include awareness and self-monitoring, willingness to accept help from others, lifestyle management, stress management, anger management, “mindfulness,” and development of resilience. Individual approaches are often promoted in an organization setting. Such programs are increasingly used for medical students and residents but must become more ingrained in clinical practice settings.

Organizational approaches include prospective identification and monitoring of worker well-being as a quality indicator, emphasis on teamwork, attention to high stress areas (such as the ICU), deliberate management of the work environment to address overwork, support for a healthy work environment in regards to respectful relationships and communication, and many others.

New call to action

What can the American College of Chest Physicians do to help alleviate burnout and enhance work-life balance among our members? I'm pleased to report that CHEST is leading an important project conducted by members of the Critical Care Societies Collaborative (CCSC), that includes leaders and experts from the American Association of Critical-Care Nurses (AACN), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and CHEST. Key goals

Continued on page 37

Impact Factor is highest in history of *CHEST*

The new Thomson Reuters Journal Citation Report Impact Factor (IF) numbers for this past year were recently released, and we are pleased to announce that the *CHEST* IF for 2014 has increased from 7.132 to 7.483, once again setting a record for *CHEST*. In addition, *CHEST*'s Eigenfactor Score (a measure that eliminates the influence of self-citations) for 2014 is 0.748, which ranks *CHEST* as 2nd in both the Respiratory and Critical Care categories of the Journal Citation Reports.

2014 Impact Factor*	2014 Eigenfactor Score**	2014 SJR	2014 SNIP
7.483	0.748	2.636	2.640
<p>Highlights:</p> <ul style="list-style-type: none"> • 4.9% increase from 2013, rising from 7.132 to 7.483 • Continues as 2nd among 27 journals in Critical Care <p>Published every year by Thomson Reuters, Impact Factor is a measure of the number of times an average paper in <i>CHEST</i> was cited in the preceding two years.</p> <p>* Journal Citation Reports®, published by Thomson Reuters, 2015.</p>	<p>Highlights:</p> <ul style="list-style-type: none"> • Now ranked 2nd in both the Respiratory and Critical Care categories of the Journal Citation Reports <p>This score eliminates the influence of self-citations. It is intended to measure the importance of a journal by considering the quality of the journal citing <i>CHEST</i>.</p> <p>** Eigenfactor® published by Eigenfactor® Project.</p>	<p>Highlights:</p> <ul style="list-style-type: none"> • Ranked in the top 5 in both Pulmonary and Respiratory Medicine and Critical and Intensive Care Medicine <p>SCImago Journal Rank is a prestige metric based on the idea that 'all citations are not created equal'. Citations are weighted, depending on the rank of the citing journal.</p>	<p>Highlights:</p> <ul style="list-style-type: none"> • Ranked 3rd in Critical Care and Intensive Care Medicine • Ranked 4th in both Cardiology and Cardiovascular Medicine and Pulmonary and Respiratory Medicine <p>Source Normalized Impact per Paper measures contextual citation impact by weighting citations based on the total number of citations in a subject field. This means SNIP values can be compared for any two journals, regardless of the field they are in.</p>

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PROFESSIONAL OPPORTUNITIES



Pulmonology Opportunity Sequim / Port Angeles, Washington

Come join us on the Olympic Peninsula in Washington State in the communities of Sequim and Port Angeles located between the Strait of Juan de Fuca and the Olympic Mountains. We are looking for a well trained BC/BE pulmonary and critical care specialist who is highly motivated and team orientated. We are a multispecialty group currently including two pulmonologists servicing a large referral area. The position will combine outpatient and inpatient pulmonary medicine. There are no Sleep Medicine responsibilities. Call and hospital coverage is shared with an outstanding hospitalist service; the position has minimal night time call responsibilities.

Nestled on the Olympic Peninsula just 70 miles northwest of Seattle, Sequim and Port Angeles have less rainfall than Seattle, virtually no commuter traffic, and provide access to abundant outdoor recreation, a wide range of community events and attractions, and easy access to Seattle and Victoria, B.C. With Olympic National Park (a world heritage site) to the south and the Strait of Juan de Fuca to the north, opportunities for camping, hiking, biking, or visiting the famous lavender fields of Sequim are limitless. Contact Nancy Buckner, CEBS, SPHR, Human Resources, Olympic Medical Center 360 417 7231. Nbuckner@olympicmedical.org.



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.

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Inpatient Pulmonary/Critical Care Position in Maine:

Join a vibrant Inpatient Pulmonary and Critical Care group of five in beautiful Maine! Central Maine Medical Center (CMMC) is seeking a BC/BE Pulmonary/Critical Care Physician to help provide pulmonary and critical care services to medical, surgical, trauma, and cardiac patients.

CMMC is a 250 bed, full service regional referral center with busy trauma, cardiothoracic, interventional radiology, vascular, and neurosurgical programs. We have a state-of-the-art 19 bed ICU and a separate 16 bed cardiothoracic unit.

Competitive salary and benefits including CME, paid vacation, student loan repayment, 403b match, and relocation fees. Work schedule revolves around a 6 day on and 6 day off philosophy, with no longer than 12 hour shifts per day. There is no outpatient clinic work.

Residents and visitors enjoy an extraordinary lifestyle that revolves around top school systems, ski resorts, lake and ocean water sports, theatre, and world-class dining.

Interested applicants may submit CV to Julia Lauer, Medical Staff Recruiter, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Email: JLauer@cmhc.org. Fax: 207/795-5696. Call: 800/445-7431. Visit our website, www.cmmc.org.

San Diego Pulmonary/ Critical Care Position

Looking for a full time physician to join our prominent Intensivist/Pulmonary Critical Care team in beautiful San Diego, minutes from downtown. Receive flexible scheduling and competitive salary. Must have valid California license.

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Pulmonary/Critical Care Physician. Pulmonary Consultants P.C. located in Phoenix Arizona is a Six-Doctor Pulmonary/Critical group seeking additional Physician due to practice growth. Diverse Hospital/office practice encompassing pulmonary, critical care medicine. Competitive salary/excellent benefits. Please send your CV via fax to 480 218-5706 or email to aliciaga@PCofMesa.com cell 480-466-2612

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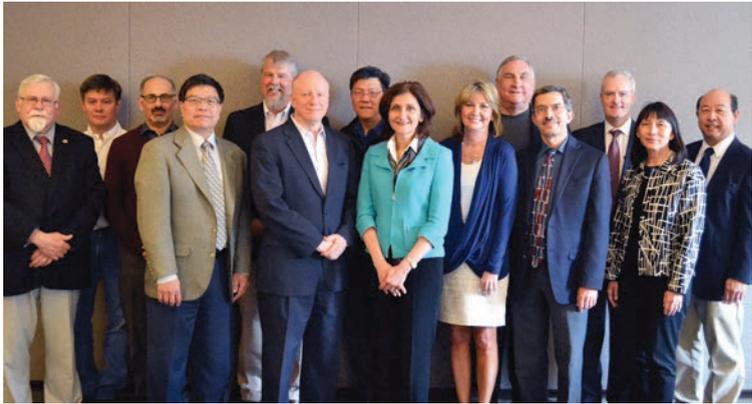
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Another look. . .

The caption was incomplete for the photo of the ABIM Pulmonary Disease Board and Pulmonary Disease Board Exam Committee that appeared in the July issue. We are republishing the image with the correct caption.



Members of ABIM's Pulmonary Disease Board and Pulmonary Disease Board Exam Committee (L-R): Dean Hess, PhD, FCCP; David E. Ost, MD, FCCP; Peter H. S. Sporn, MD, FCCP; Kevin M. Chan, MD, FCCP; John Allen Cooper, MD; Charles W. Atwood, MD, FCCP; David Au, MD; Serpil C. Erzurum, MD, FCCP; Tommye Lambert, MBA, MDIV; John H. Hansen-Flaschen, MD, FCCP; Nizar N. Jarjour, MD, FCCP; Michael E. Nelson, MD, FCCP; Lynn T. Tanoue, MD, FCCP; and Stanton T. Siu, MD, FCCP. Not pictured are Francis X. McCormack, MD and Mindy S. Shapiro, MD, FCCP.

This month in *CHEST*: Editor's picks

BY DR. RICHARD S. IRWIN,
MASTER FCCP

Hydronic Fracturing (Fracking) and the Clean Air Act. *By Dr. R. B. Evans et al. (Editorial)*

Organ Donors: Making the Most of What Is Offered. *By Drs. S. D. Nathan and C. S. King. (Editorial)*

Unraveling the Pathophysiology of the Asthma-COPD Overlap Syndrome: Unsuspected Mild Centrilobular Emphysema Is Responsible for Loss of Lung Elastic Recoil in Never Smokers With Asthma With Persistent Expiratory Airflow Limitation. *By Dr. A. F. Gelb et al.*

Editorial - Elastic Recoil Revisited. *By Dr. K. Rabe.*

Adult Bronchoscopy Training: Current State and Suggestions for the Future: CHEST Expert Panel Report. *By Dr. A. Ernst et al.*

Editorial - Learning to Look Through the

Bronchoscope. *By Dr. M. J. Simoff*
Acid and Weakly Acidic Gastroesophageal Reflux and Pepsin Isoforms (A and C) in Tracheal Secretions of Critically Ill Children. *By Dr. C. Hallal et al.*



Continued from page 34

of this task force are to raise awareness and set the stage for interventions to reduce burnout in the ICU through publication of a review and call to action in multiple journals; sponsorship of educational sessions at our annual meetings; and development and posting of additional Web-based tools and resources. While critical care workers are certainly aware of the importance and prevalence of ICU burnout, an important aim is to raise awareness among other key groups, including policymakers, administrators, and funding agencies.

In conclusion, please take a moment during this month of August to pause and consider your own work-life balance and how, together, we can enhance not just the health of our patients but also the personal well-being and long productive career among those who care for the critically ill and injured.

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Satisfy your educational needs, your taste buds with CHEST 2015

S smoked meats, bagels, poutine, duck confit, couscous...Montréal has it all! When you travel to Montréal, October 24-28, for the CHEST Annual Meeting 2015, expect to fill up on clinical education opportunities and diverse cuisine.

While Montréal offers high end French fare, casual plates at diners, and everything in between, the city is best known for some simple staples. Bagels are iconic in Montréal. These special bagels are hand-rolled, blanched in honey water, and baked in a wood-burning oven. You can taste these Montréal classics at St. Viateur Bagel or Fairmount Bagel. The bagel shops are located a block apart in the Mile End neighborhood of Montréal.

Smoked meat is also popular. Many restaurants serve smoked meat sandwiches, but if you want to take a foodie's tour of the city, Schwartz's is the place to go. Founded in 1928, this deli dishes up a classic brisket on rye. You can find this landmark in the Le Plateau-Mont-Royal neighborhood.

And you can't visit Québec without feasting on poutine. Indulge with Foie Gras Poutine, fried French fries in duck fat with a slab of foie gras on top. Find this dish at Au Pied de Cochon, chef Martin Picard's restaurant, located in the Le Plateau-Mont-Royal neighborhood.

We checked with our favorite Montréalers, CHEST members, for their favorite spots:

- Bouillon Bilk - Treat yourself to a fine-dining experience with delicious contemporary

cuisine, focusing on seafood. *located at 1595 Boulevard Saint-Laurent, Montréal, H2X 2S9*

- le Majestique - This restaurant and bar offers many small plate options. *located at 4105 Boulevard Saint-Laurent, Montréal, QC H2W*

- Brasserie T - Catch a show at the nearby Place des Arts, and then treat yourself to this French cuisine. *located at 1425 Rue Jeanne-Mance, Montréal, QC H2X 2J4*

- Graziella - Located 10 minutes walking distance from the Palais des Congrès, this restaurant is known for their upscale Italian dishes. *located at 116 Rue McGill, Montréal, QC H2Y 2E5*

- Le filet - This hot spot features glam decor and creative seafood-focused dishes along with a seasonal terrace. *located at 219, ave. Mont-Royal Ouest, Montréal, QC H2T 2T2*

- Pasta Casareccia - Try fresh homemade pastas and sauces at this trattoria plus deli. *at 5849 Rue Sherbrooke Ouest, Montréal, QC H4A 1X4*

CHEST 2015 will also offer you a variety of educational options including hands-on simulation, case- and problem-based presentations, small-group interactive discussions, lectures, self-study opportunities, and more. CHEST 2015 is dedicated to delivering the latest information in pulmonary, critical care, and sleep medicine to you, ensuring you make the best decisions with your patients. Register by August 31 to pay the lowest fees. Learn more at chestmeeting.chestnet.org.

NETWORKS: New name, quality initiatives, transplants, PLLR rule

Home Care

What's in a name?

Since its early inception, the Home Care NetWork was created to share expertise at home. Initially, this was uncommon and largely in survivors of the polio epidemics. Today, home-based ventilation is given for a wide variety of diseases, including neuromuscular diseases, chronic lung diseases, central hypoventilation syndromes, spinal cord injuries, and many others.

The Home Care NetWork has been renamed the Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork.

The number of individuals has been growing exponentially. Even over the last 10 to 20 years, this growth has continued both domestically and internationally. As just one example, the largest pediatric home ventilation program in Canada saw an increase from two children in 1991 to 156 in 2011 (Amin et al. *Pediatr Pulmonol.* 2014;49:816). At the same time, support is being increasingly provided with noninvasive ventilation, including up to 24-hour ventilator requirements, and new equipment and skills are being developed on a regular basis to facilitate this support.

There are also many challenges that accom-

pany this growing population. One priority our steering committee has repeatedly heard is that patients with progressive neuromuscular diseases, especially in adulthood, are having difficulties finding clinicians to provide appropriate noninvasive ventilation. And even when they do and are well cared for, they risk receiving a tracheostomy when they are admitted to hospitals after admissions for acute decompensations, despite experience and literature suggesting this is often avoidable.

We have also come to realize that CHEST members seeking out resources in this area have not always known what the Home Care NetWork did. As such, to continue to provide and improve the support to the CHEST community, the Home Care NetWork has been renamed the Home-Based Mechanical Ventilation and Neuromuscular Disease NetWork.

Dr. David Zielinski, FCCP
Vice-Chair

Practice Operations

Changes to our practice climate

Health-care providers continue to hear reports on the initiatives underway to change the cost curve and increase the value of health care. CMS continues its efforts with meaningful use, PQRS, and value-based payment modifiers.

Eligible providers' performance in 2015 is

being assessed for payment adjustments to be phased in yearly from large groups in 2015 to all providers by 2017. Individual CMS beneficiaries are being assigned to physician groups using stepwise methodology and tax identification numbers of providers to track quality and cost performance.

For years, hospitals have been attuned to the needs to optimize quality and cost performance for populations of CMS patients. Physician groups similarly must now focus on process improvement to align with CMS goals for quality and cost for both inpatient and outpatient care. In doing so, payments to those provider groups from CMS will be adjusted upwards, be held neutral, or adjusted downwards based upon their success.

If you are interested in assisting your colleagues in preparing for changes to our practice climate like those outlined above, we welcome you to join the Practice Operations NetWork. For those interested, please contact networks@chestnet.org, or simply drop in and visit us at CHEST 2015 during our NetWork Featured Lecture - Comparing the Canadian Healthcare Model to the US Model on Tuesday, October 27, in Montreal! We hope to see you there!

<http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeedbackProgram/valuebasedpaymentmodifier.html>

Dr. Chad Case, FCCP
Steering Committee Member

Early Registration Ending August 31!

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800/343-2227 or 224/521-9800

This Is Going to Be **BIG**

Join us in Montréal for CHEST 2015, your connection to learning opportunities that will help optimize the clinical decisions you make. We've packed as many education deliverables as we can into 4 days to make the **BIGGEST** impact on your professional development and patient care. We'll offer a full schedule of sessions that address topics from an interdisciplinary and interprofessional perspective to ensure a comprehensive (and **BIG**) understanding of chest medicine.

And, our international faculty and attendees will give you a worldwide viewpoint on clinical issues. It doesn't get much **BIGGER** than that!


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Interdisciplinary Programs

Bring your entire care team to attend programs that will address clinical issues across the disciplines. Session speakers will represent each role and present from their respective perspective, so your group can collectively experience practical, relevant updates.

Great Beginnings

Start Sunday and Monday by attending the opening sessions with keynote speakers Daniel H. Pink, author of *A Whole New Mind* and Drive, and Farzad Mostashari, MD, MSc, CEO of Aledade, a start-up he co-founded to help primary care doctors form accountable care organizations.

CHEST Simulation Center

Enhance your skills in a hands-on clinical environment. Work with expert faculty to sharpen your skills and apply your knowledge using real equipment and simulators.

More MOC at CHEST 2015

We're planning to offer more MOC opportunities than ever before. CHEST plans to submit a wider variety of activities to ABIM for acceptance for MOC credit. Watch for details.

Plenty of Extras

- Original Investigations
- Global Case Report Posters
- Affiliate and Medical Student/ Resident Case Reports
- Self-study Modules
- GAMEs: Games Augmenting Medical Education

New This Year

Team Up to Advance Patient Care: Interdisciplinary Programs

This year, more than ever, we want you to bring your entire care team. Our all-new interdisciplinary program will feature sessions that dive deep into topics from a multidisciplinary, multiprofessional perspective. Your group can attend together to learn comprehensive, practical updates relevant to each member on the team.

Register your team as a group and save. See chestmeeting.chestnet.org for details.



Transplant

Lung transplantation and the quest for donor lungs

With improving survival rates and increasing recognition of quality-of-life benefits, more patients are being referred and listed for lung transplantation. However, each year, patients die while awaiting lung transplantation. Obtaining enough suitable donor lungs remains a challenge.



DR. LEARD

Potential donor lungs are declined for many reasons, one of which is concerns about quality. The best way to accurately assess and predict a deceased donor lung's function remains unknown.

Although more marginal donors are now considered and used based on the study by Ware and colleagues in 2002 (Lancet. 2002;360[9333]:619), further research is needed to better assess the lungs declined today.

Several strategies are being pursued to expand the availability of donor lungs. There has been expanding recognition that lungs from donors after cardiac death (DCD) can be used successfully. About 15% of US donors are now DCD donors (UNOS Data Trends 2014 from www.unos.org), and these are an important source of potential donor lungs.

Ex vivo lung perfusion (EVLV) techniques may help to further assess and potentially repair donor lungs that might have otherwise been considered

About 15% of US donors are now DCD donors, and these are an important source of potential donor lungs.

marginal or declined. Although not yet approved for widespread use, lungs that may have been declined for concerns about quality may soon have a chance to be further evaluated on EVLP systems.

Ongoing research focusing on improved strategies for procuring lungs from DCD donors and for rehabilitating donor lungs on EVLP should lead to increased availability of donor lungs. Perhaps soon, every listed patient may be offered a chance for a successful lung transplant.

Dr. Lorianna Leard, FCCP
Steering Committee Member

Women's Health

FDA pregnancy risk classification system removed

As of June 30, 2015, the US FDA removed the well known A, B, C, D, and X pregnancy risk classification system for prescription drugs and biological products [FDA HHS. Fed Regist. 2014;79(233):72063] The old classification system did not always consistently communicate differences in fetal risk and failed to take into account the risk of the untreated condition, resulting in a tendency to oversimplify risk assessment of drug safety in perinatal women. The new "Pregnancy and Lactation Labeling Rule" (PLLR) requires the elimination of the letter

categories from labeling and may impact over 6 million women taking prescription medication during gestation.

The PLLR includes three subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential. The PLLR mandates that labeling include data on dosing and potential fetal risks. Although previously not required, manufacturers must now provide information about pregnancy exposure registries that collect and maintain data on pregnant women when available.

The lactation subsection includes information about the amount of drug in breast milk and potential effects on breastfed infants. A new subsection includes information about pregnancy testing, contraception, and infertility.

The PLLR does not affect over-the-counter medicines, and medications that were approved after June 30, 2001 will be phased in gradually. With the new format and additional data, health-care professionals are able to better inform and counsel patients requiring medication during pregnancy or while breastfeeding, while allowing greater numbers of women to participate in registries designed to collect data on a patient population often under-represented in research studies.

CAPT Janet Myers, MC, USN, FCCP
Ex Officio

The opinions herein are those of the author and do not necessarily represent those of the Department of the Navy, the Department of Defense, or the United States government.

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7.483**



The 2014 Journal Citation Reports data from the ISI Web of Knowledge show the *CHEST* Impact Factor is 7.483, the highest in the journal's history. In addition, *CHEST* ranks 2 of 27 journals in the Critical Care Medicine category and 5 of 54 in the Respiratory Systems category.

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