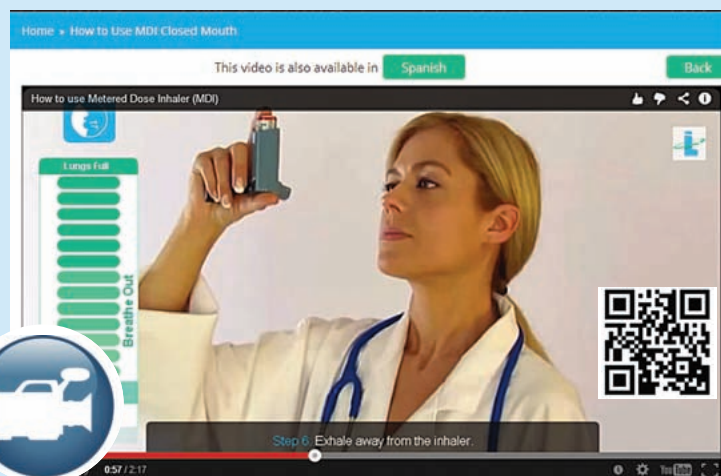


# CHEST™ Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

## Patient resources



Videos providing detailed demonstrations of how to properly use various inhaler devices are among asthma and COPD education resources offered online by The CHEST Foundation. Scan the code to visit [chestphysician.org](http://chestphysician.org). See page 19 for more details.

## Acetaminophen in ICU may be renoprotective

BY M. ALEXANDER OTTO  
*Frontline Medical News*

SAN DIEGO – Three days of acetaminophen seemed to lower creatinine levels in severely septic patients, suggesting a renoprotective effect, according to results from a phase II study out of Vanderbilt University in Nashville, Tenn.

Investigators there randomized 18 septic ICU patients to acetaminophen 1 g every 6 hours for 3 days and 22 patients to placebo, both delivered by mouth or feed-

ing tube. The patients had all been in the ICU for less than 24 hours, and had detectable levels of plasma cell-free hemoglobin (CFH).

The findings were presented at an international conference of the American Thoracic Society.

CFH has been associated with death in a number of conditions. The iron separates, radicalizes, and causes oxidative injury, especially to the kidneys. Acetaminophen chemically reduces the iron, and has been shown to

See **Renoprotection** • page 16

## For stable PE, thrombolysis may reduce mortality

*Future could hold shift in treatment.*

BY MARY ANN MOON  
*Frontline Medical News*

**T**hrombolytic therapy decreased all-cause mortality in patients with hemodynamically stable pulmonary embolism associated with right ventricular dysfunction – those at “intermediate risk,” according to a meta-analysis in JAMA.

The investigators described their study of 16 randomized, controlled clinical trials involving 2,115 patients as “the first analysis of thrombolysis in PE that has sufficient statistical power to detect associations with a meaningful mortality

reduction.” If their findings are confirmed in future randomized clinical trials, “there may be a shift in the treatment of selected patients with intermediate-risk PE using thrombolytics.”

However, “the optimism regarding this clinical advantage must be tempered by [our] finding of significantly increased risk of major bleeding and intracranial hemorrhage associated with thrombolytic therapy, particularly for patients older than 65 years,” said Dr. Saurav Chatterjee of the division of cardiology, St. Luke’s-Roosevelt

See **Thrombolysis** • page 7

## New push: OSA screen at Medicare intro

BY ALICIA AULT  
*Frontline Medical News*

MINNEAPOLIS – The American Academy of Sleep Medicine is pushing to have a simple sleep apnea questionnaire included in the initial Welcome to Medicare preventive care visit.

Including such a screening tool would help identify obstructive sleep apnea (OSA) when patients first join the Medicare program and thus improve the odds of diagnosing and treating the condition, said Dr. Timothy Morgenthaler, president of the AASM. Getting a handle

on OSA could also reduce the potential that the beneficiary will develop related chronic conditions, and that will help Medicare curb expenditures, he said.

An estimated 20% of current Medicare beneficiaries

See **Initial visit** • page 31

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2014

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Pulmonary  
Medicine  
August 27-31



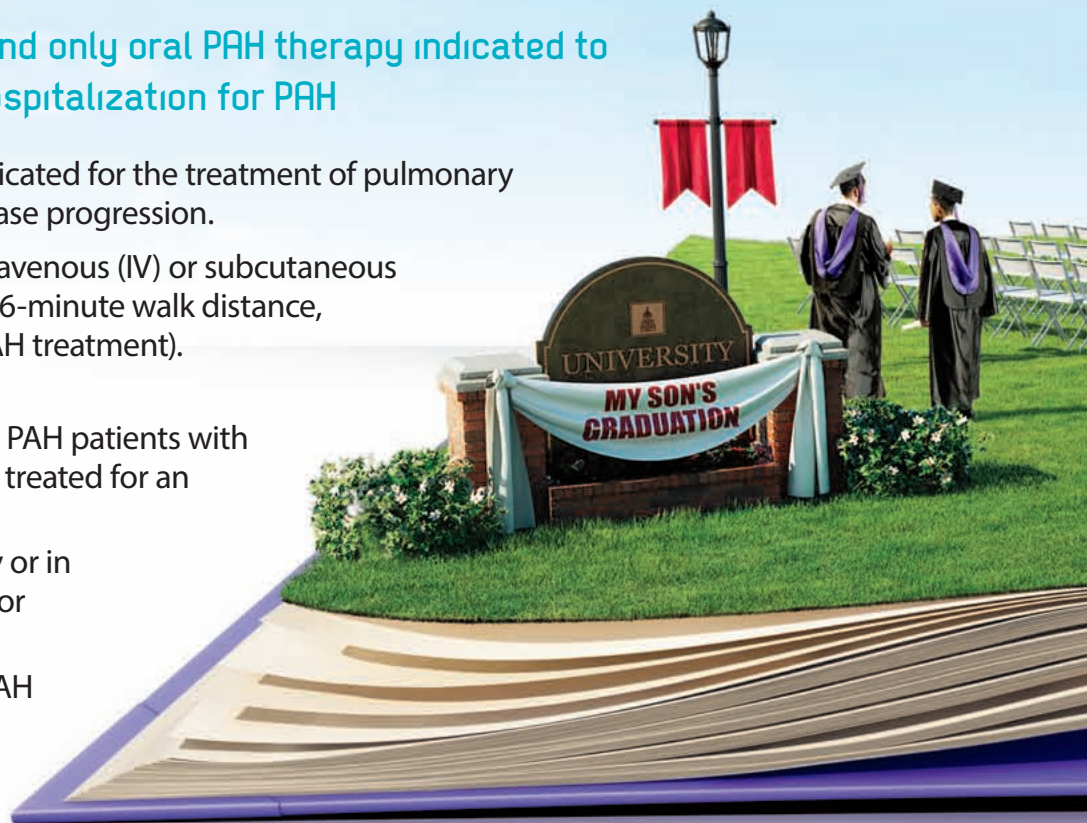
[boardreview.chestnet.org](http://boardreview.chestnet.org)

# HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

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.

### Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study  $>3 \times \text{ULN}$  were 3.4% for OPSUMIT vs 4.5% for placebo, and  $>8 \times \text{ULN}$  were 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





Patient dramatization

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 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.

#### 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.

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

FUTURE.  
FORWARD. | **Opsumit**  
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](http://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.

#### OPSUMIT® (macitentan)

#### 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.

**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%

#### 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)].



## OPSUMIT® (macitentan)

### 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.

## OPSUMIT® (macitentan)

### Drug Interactions

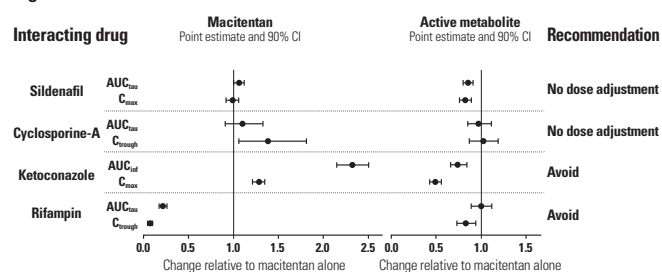
#### *In vitro studies*

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.  
5000 Shoreline Court, Ste. 200  
South San Francisco, CA 94080, USA  
ACT20131018

**Reference:** 1. OPSUMIT full Prescribing Information. Actelion Pharmaceuticals US, Inc. October 2013.  
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# Anatomic segmentectomy looks as good as lobectomy

BY MARY ANN MOON

Frontline Medical News

**P**atients with stage I non-small cell lung cancer who underwent anatomic segmentectomy had similar outcomes to those who underwent lobectomy in a large propensity-matched trial comparing the two approaches, which was reported in the *Journal of Clinical Oncology*.

Long-term survival and recurrence rates, as well as perioperative morbidity and mortality, were not significantly different between the two groups of patients, even though lobectomy is considered the gold standard of treatment for early-stage non-small cell lung cancer (NSCLC), said Dr. Rodney J. Landreneau of the department of cardiothoracic surgery, University of Pittsburgh

Medical Center, and his associates.

If the results of this retrospective single-center study are validated in future prospective, multicenter, randomized controlled trials, "anatomic segmentectomy should be considered as a valid alternative to lobectomy in properly selected patients," the investigators noted.

The investigators identified 392 patients in their center's lung cancer database who had anatomic segmentectomy and 800 who had lobectomy, then performed propensity matching to account for the confounding effects of patient age, sex, smoking status, and forced expiratory volume in 1 second (FEV<sub>1</sub>) level; tumor size; and patient history of hypertension, chronic obstructive pulmonary disease, diabetes, gastroesophageal reflux, coronary artery disease, and other types of cancer. They then assessed outcomes in 624 propensity-

matched patients: 312 who had segmentectomies (cases) and 312 who had lobectomies (controls).

Approximately 93% of the study cohort were current or former smokers. The mean patient age was 68.5 years at baseline. The mean tumor size was 2.2 cm. The participants were followed for a median of 5.4 years.

Overall survival was 54% for cases and 60% for controls, a nonsignificant difference. Both locoregional recurrence rates and distant recurrence rates also showed no significant difference by treatment type. Perioperative morbidity and mortality slightly favored anatomic segmentectomy, but not significantly so, Dr. Landreneau and his associates reported (*J. Clin. Oncol.* 2014 June 30 [doi:10.1200/JCO.2013.50.8762]).

Further analyses demonstrated that anatomic segmentectomy was not a

predictor of recurrence or of survival.

Surgeons excised a greater number of lymph nodes with lobectomy (median, 12 nodes) than with anatomic segmentectomy (median, 6 nodes). However, the number of lymph node stations assessed was the same in both groups (a median of three in each), and the proportion of cancers that required upstaging at surgery was not significantly different between cases (29.5%) and controls (36.5%).

Multicenter prospective randomized trials comparing the two approaches are needed to confirm these findings; two are underway, researchers said.

This study was supported in part by the National Institutes of Health and the Thoracic Surgery Foundation for Research and Education. Dr. Landreneau reported no financial conflicts; two of his associates reported industry ties.

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### CHEST PHYSICIAN Is Online

*CHEST PHYSICIAN is available on the Web at [chestphysician.org](http://chestphysician.org).*

## Trial seeks to match treatments to tumor profiles

**A** phase II/III trial using genomic profiling to match patients with investigational treatments began recruiting patients with advanced squamous cell lung cancer in June.

The Lung-MAP (Lung Cancer Master Protocol) trial is a public-private collaboration among the National Cancer Institute (NCI), SWOG Cancer Research, Friends of Cancer Research, the Foundation for the National Institutes of Health, Foundation Medicine,

and five pharmaceutical companies.

Lung-MAP is expected to enroll 10,000 patients and be completed in 2022. To be eligible, patients will have progressed after receiving exactly one front-line, platinum-containing metastatic chemotherapy regimen. Between 500 and 1,000 patients will be screened per year for more than 200 cancer-related gene alterations. Based on the tumor profiles, all patients will then be assigned to one of

five initial treatment arms, testing four investigational targeted treatments and an anti-PD-L1 immunotherapy.

The trial will be conducted at more than 200 medical centers. As many as five to seven additional drugs may be evaluated over the next 5 years, the press release said. Information on enrolling patients can be found on the trial website: [www.lung-map.org](http://www.lung-map.org).

— Laura Nikolaidis

## CHEST Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

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**POSTMASTER:** Send change of address (with old mailing label) to CHEST PHYSICIAN, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

**CHEST PHYSICIAN** (ISSN 1558-6200) is published monthly for the American College of Chest Physicians by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Subscription price is \$230.00 per year. Phone 973-206-3434, fax 973-206-9378.

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# Variation in admission rates from EDs raises eyebrows

BY BRUCE JANCIN  
*Frontline Medical News*

DALLAS – Emergency departments across the United States vary widely in their admission rates for the 15 most common medical and surgical conditions resulting in hospitalization.

The variability is important from a cost perspective because ED admission is increasingly the dominant route by which patients enter the hospital, Dr. Keith E. Kocher observed at the annu-



**'The Big-5 high-variation/low-mortality conditions represent the greatest source of potential savings.'**

DR. KOCHER

al meeting of the Society for Academic Emergency Medicine. "We're talking about potentially billions of dollars that may be in play if we narrow these differences." The 15 conditions collectively account for more than \$266 billion/year in hospital charges to payers.

Dr. Kocher, an emergency medicine physician at the University of Michigan, Ann Arbor, and his colleagues conducted a retrospective analysis of the Nationwide Emergency Department Sample for 2010. This database, maintained by the Agency for Healthcare Research and Quality (AHRQ), contains records on the millions of ED visits at nearly 1,000 hospitals in 28 states.

Their analysis adjusted for the severity of case mix by incorporating demographics, comorbid conditions,

primary payer, median income, and patient zip code. The researchers then determined risk-standardized admission rates – the number of predicted admissions for each ED given the institutional case mix, divided by the number of expected admissions had those patients been treated at the average ED, multiplied by the mean admission rate for the sample.

The five disorders with the least variation in admission rates among the 15 most commonly admitted conditions were heart failure, stroke, acute renal failure, acute MI, and sepsis. All are characterized by relatively high inpatient mortality. (See chart for the disorders with the greatest variation.)

"High-mortality/low-variation diagnoses like sepsis and MI provide little opportunity to realize meaningful spending reductions. Instead, the Big-5 high-variation/low-mortality conditions represent the greatest source of potential savings," Dr. Kocher said.

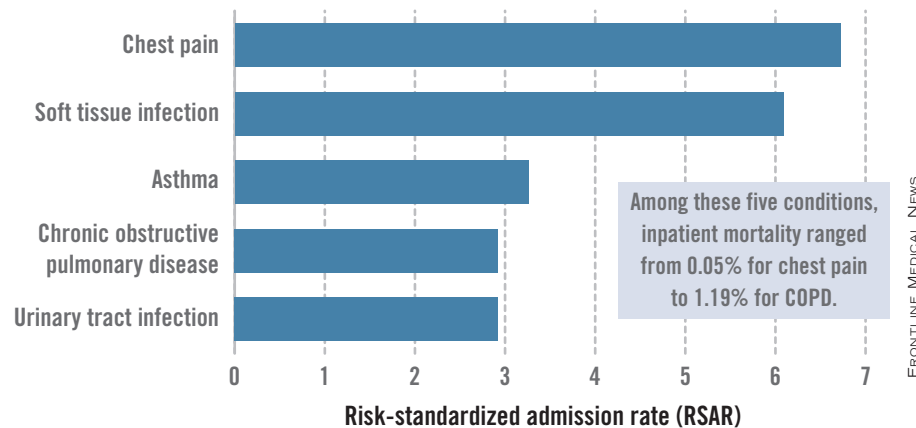
If EDs with high risk-standardized admission rates above the median reduced admissions for the five high-variation/low-mortality conditions to the median rate, it would save an estimated \$16.9 billion in charges and \$5.1 billion in costs per year.

Incentivizing top quartile and bottom quartile EDs to meet the median rate would yield an estimated \$2.8 billion reduction in charges and a \$0.8 billion decrease in costs per year.

The in-hospital mortality implications of moving admission rates toward the median are not known, Dr. Kocher acknowledged. "We're not implying that we know the optimal rate of admission. In fact, it probably varies from condition to condition."

Further, a formal economic analysis of net expenditures would need to

The five conditions with the largest variations in risk-standardized admission rates had the lowest mortality



**Note:** The analysis focused on the top 15 conditions admitted from the ED during 2010, using data from the Nationwide Emergency Department Sample.

**Source:** Dr. Kocher

incorporate the increased outpatient expenditures of shifting care to ambulatory settings, he said.

The study was supported by

AHRQ. Dr. Kocher reported having no financial conflicts.

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## VIEW ON THE NEWS

**Dr. Daniel Ouellette, FCCP, comments:** Health care professionals are beginning to appreciate the maxim that those in technology and industry sectors have known for years: Reduction in variance leads to improvement in quality. When this maxim is applied to the subject of hospital admission after an encounter in the ED, we find that a "good news-bad news" scenario exists.

A recent study examining admission rates after an ED visit for the 15 most common diagnoses finds a low

variance in admission rates across the country for those diagnoses with a high mortality. On the other hand, those diagnoses with a low mortality had a high variance in admission rates. Can we improve quality and cost by reducing variance in admission rates for these disorders? The authors of this study suggest that costs will be improved substantially by reducing variance. I suspect that this will only happen (and should only happen!) if the optimal admission rates for quality care are low ones.



## Treating stable PE

Thrombolysis from page 1

Hospital Center of the Mount Sinai Health System, New York, and his associates (JAMA 2014;311:2414-21).

The study population included 1,499 patients who had hemodynamically stable PE associated with right ventricular dysfunction, the largest subset of patients seen in clinical practice and the group for whom the risks and benefits of thrombolysis are the most unclear.

After a mean follow-up of 82 days, overall mortality was 2.17% in patients who received thrombolysis, compared with 3.89% in those who received anticoagulation. In addition, the risk of recurrent PE was significantly lower with thrombolytic therapy

(1.17%) than with anticoagulation (3.04%).

However, the rate of major bleeding was 9.24% for thrombolytic therapy, compared with 3.42% for anticoagulation. And the rate of intracranial hemorrhage was 1.46% for thrombolysis, compared with 0.19% for anticoagulation, the investigators said.

The bleeding risk was especially high in patients aged 65 years and older. Attenuation of this risk in younger patients suggests that they may be considered stronger candidates for thrombolytic therapy, Dr. Chatterjee and his associates said.

Dr. Chatterjee reported no financial conflicts; his associates reported ties to AstraZeneca, Boston Scientific, Cardiostem, Cordis, EKOS Corporation, Embolitech, GenWay, Johnson & Johnson, Soteria, and Vascular Magnetics.

## VIEW ON THE NEWS

**Dr. Joshua A. Beckman comments:** Dr. Chatterjee and his associates calculated the net clinical benefit of thrombolysis, and their result "suggests evidence of modest efficacy in intermediate-risk PE."

But their findings do not yet add up to a change in the standard of care. Each clinician must decide on an individualized basis which of these patients should re-

ceive thrombolytic therapy, based on clinical presentation, comorbid conditions, and both the physician's and the patient's tolerance of risk.



Dr. Beckman is in the cardiovascular division at Brigham and Women's Hospital, Boston. He reported various ties to industry. These remarks were taken from his editorial accompanying Dr. Chatterjee's report (JAMA 2014;311:2385-6).

# Different zolpidem regimens show similar efficacy

BY SUSAN LONDON

Frontline Medical News

MINNEAPOLIS – People with chronic insomnia don't have to take the sedative-hypnotic agent zolpidem every night for it to remain efficacious, a randomized trial found.

Investigators enrolled in the trial 56 patients who had had a response to a priming phase of 4 weeks of nightly zolpidem (Ambien) 10 mg and assigned them to three maintenance strategies: nightly dosing, intermittent dosing (whereby the drug was taken 3-5 nights per week of the patient's choice), and partial reinforcement dosing (whereby a capsule was



**Interspersing placebos between active doses appears to be reasonable for maintaining clinical gains.**

DR. PERLIS

taken every night, but half were placebos).

Use of partial reinforcement after a priming phase, during which the drug is repeatedly paired with sleep, taps into the phenomenon of conditioning, explained lead author Michael Perlis, Ph.D., director of the behavioral sleep medicine program, University of Pennsylvania, Philadelphia. "In this kind of paradigm, on the nights when there is no medication, they are getting a conditioned response; on the nights when there is medication, you are reinforcing the capsule as the conditioned stimulus for that physiologic response."

Analyses based on the 41 compliant patients showed that after 1 month, the three maintenance regimens were statistically indistinguishable in terms of measures such as time to relapse, sleep latency, and waking after sleep onset.

Total sleep time was significantly longer with nightly dosing (463 minutes) and partial reinforcement dosing (459 minutes) than with intermittent dosing (429 minutes). Also, sleep efficiency was significantly better with nightly dosing (90%) and partial reinforcement (91%) than with intermittent dosing (88%).

The frequency of medical symptoms, possibly adverse effects, was statistically indistinguishable across groups, although they tended to be least frequent with the partial reinforcement strategy and most with

the intermittent dosing strategy.

"The present findings suggest that in compliant subjects, any of the three 10-mg strategies evaluated may be used to maintain treatment response over time. If a trend is evi-

dent, it's that subjects in the intermittent dosing group condition do not do as well as nightly dosing and as in partial reinforcement, and that's especially and significantly true for total sleep time and sleep efficiency,"

Dr. Perlis commented. "The take-home message is interspersing placebos between active doses appears to be a reasonable approach for maintaining clinical gains following priming, in other words, obtention of

**Approximately 50% of individuals with narcolepsy are undiagnosed.<sup>1</sup>**



**Narcolepsy symptoms may be lurking beneath the surface.**

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JP-116-01 Rev0613



## VITALS

**Key clinical point:** Interspersing placebos between active doses may be a reasonable approach for maintaining clinical gains following priming.

**Major finding:** Zolpidem remained similarly efficacious over 1 month whether given nightly, intermittently, or interspersed with

placebos. But the last strategy tended to have the lowest frequency of adverse effects.

**Data source:** A randomized trial of 56 patients with chronic insomnia who had a response to zolpidem during a priming phase

**Disclosures:** Dr. Perlis disclosed no relevant conflicts of interest.

treatment response with a full-dose strategy.”

In upcoming research, the investigators plan to see how low they can go with the partial reinforcement strategy as far as nights of zolpidem – even down to zero capsules of active drug – and still

maintain the benefit of nightly dosing. If this proves successful, “then it may be possible to one, maintain treatment response for long periods of time with fractional amounts of medication. Second, we have a potential to reduce tolerance and side effect risks. Third, we would massively be able to reduce the cost of maintenance therapy considering placebos are basically free,” he said.

“Finally and most important, ... if this approach works as applied to insomnia, it may be a powerful tool for the management of medications with narrow therapeutic indices. Put differently, the partial reinforcement approach may be a strategy for managing medications that have nearly as much risk as they do benefit. That’s where the money is,” said Dr. Perlis, who disclosed no relevant conflicts of interest.

In an interview, Brandy Roane, Ph.D., one of the session cochairs and a psychologist at the University of North Texas Health Science Center in Fort Worth, noted that the study is interesting in that it sheds light on why patients on intermittent dosing might become increasingly dependent on the medication.

“You have the patient who becomes more likely to increase their use even if it’s not effective, because they end up taking that dose on the night when they do sleep better because it would be a typical what we call crash night, where their body is already so physically fatigued and their homeostatic sleep pressure is so increased that they take it and it pairs it with that [sleep], and it’s a learned response: ‘I took medication and I slept so much better.’ Whereas if you hadn’t paired it with that, they would have slept better anyway,” she explained.

“So I think it does look more at that real world type of setting and starts to speak to some of that possible use actually increasing the likelihood that they are going to take the medication, whether it’s effective or not, and then not use behavioral interventions that might be more effective.”

Colin A. Espie, Ph.D., the other session cochair and a professor of sleep medicine in the Nuffield Department of Clinical Neuroscience at the University of Oxford, England, commented: “This is theoretically quite an interesting study. I think there might be some ethical problems in devising a practice whereby you systematically give people placebo without their knowledge, so I’m not sure it’s a very usable clinical strategy. But I think it’s an interesting paradigm to understand more about the placebo effect.”

## To identify the symptoms of narcolepsy, LOOK DEEPER

**C** **Cataplexy:** A sudden, temporary loss of muscle tone triggered by strong emotions<sup>1,2</sup>

**H** **Hypnagogic Hallucinations:** Vivid dream-like experiences that occur during the transitions between wake and sleep<sup>1,2</sup>

**E** **Excessive Daytime Sleepiness:** The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep<sup>2</sup>

**S** **Sleep Paralysis:** The temporary inability to move or speak while falling asleep or waking up<sup>2</sup>

**S** **Sleep Disruption:** The interruption of sleep by frequent awakenings<sup>1,2</sup>

C.H.E.S.S. is a useful mnemonic for recalling the 5 symptoms of narcolepsy,<sup>3</sup> although not all patients experience all symptoms.<sup>2</sup> Narcolepsy is primarily characterized by excessive daytime sleepiness and cataplexy.<sup>2</sup> All patients with narcolepsy have excessive daytime sleepiness.<sup>2</sup> The presence of cataplexy is pathognomonic for narcolepsy.<sup>2</sup>

### Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder<sup>2,3</sup>

Narcolepsy is a chronic, life-disrupting neurologic disorder in which the brain is unable to regulate sleep-wake cycles normally, resulting in sleep-wake state instability.<sup>1-4</sup>

### Narcolepsy Is Underdiagnosed

It is estimated that approximately 50% or more of individuals with narcolepsy remain undiagnosed.<sup>1</sup> Initial onset of symptoms typically occurs between the ages of 15-25,<sup>2</sup> although an accurate diagnosis can take more than 10 years.<sup>1</sup>

### Narcolepsy Symptoms Can Be Difficult to Recognize

Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.<sup>1,2</sup> The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.<sup>1,2,5</sup> Individual symptoms should be evaluated carefully to determine whether they are due to narcolepsy or another condition. Looking deeper at the symptoms can help healthcare professionals establish a differential diagnosis.

Get a Deeper Look, at [www.NarcolepsyLink.com](http://www.NarcolepsyLink.com)

Narcolepsy Link contains resources to help identify narcolepsy symptoms and facilitate communications with your patients.



# ICD-10 delay: Proceed with caution, experts advise

BY MARY ELLEN SCHNEIDER

Frontline Medical News

When it comes to ICD-10 readiness, invest in low-cost, high-impact steps that will benefit the October 2015 switch to new code set, but will also improve the general health of the medical practice.

Now that implementation of ICD-10 has been delayed a full year, “I’d avoid spending too much money at this stage,” said Robert Tennant, senior policy adviser at the Medical Group Management Association.

Practical steps include checking claims already paid under ICD-9 to see whether the documentation was sufficient to assign an ICD-10 code. In the case of a sprained wrist, for example, make sure the documentation includes whether the injury was to the left or the right wrist, Mr. Tennant explained.

Consider dual coding – coding the same claims in both ICD-9 and ICD-10 – for some most commonly used codes, Mr. Tennant advised. If you “go through the clinical documentation improvement exercises, you will produce a better quality medical record and that can help the practice in a number of ways even if ICD-10 never goes forward.”

Other low-cost, high-impact steps include reaching out to clearinghouses to request reports on the practice’s top diagnosis codes, the top pended or rejected claims, and the most fre-

quently used unspecified codes.

“That should really focus the practice in on those claims that are the most problematic,” he said.

One tough decision is when to upgrade software. Upgrade too early and the practice could lose money if there’s another delay. Wait too long and the practice risks being unprepared for the compliance date, Mr. Tennant said. He advised finding out when the vendor will be ready with upgrades and how long it will take them to install the software and provide training. Use that to build an implementation timeline.

“It’s such a tightrope that practices have to walk,” Mr. Tennant said.

Dr. George Abraham, who is part of a six-physician practice in Worcester, Mass., was ready for ICD-10 to take effect this year. His practice spent more than \$25,000 preparing for the scheduled switch and had done some initial testing of systems when the delay was announced.

Now the practice faces an additional expenditure on upgrades and refresher courses for coders and physicians.

“After everything, poof, it’s gone in a puff of smoke because everything came to a standstill when ICD-10 got suspended for a year,” said Dr. Abraham, governor of the Massachusetts chapter of the American College of Physicians. “It will be déjà vu all over again come summer of next year. We’ll be doing the same thing in preparation for ICD-

10 being rolled out in October 2015.”

Most health plans won’t begin end-to-end testing of claims until next year, Dr. Abraham said, and that’s worrisome, as it may not provide enough time to work out potential glitches.

“A delay in claims being processed is our biggest anxiety,” he said. “A delay in payments will lead to a severe cash flow crunch.”

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## VIEW ON THE NEWS

**Dr. James A.L. Mathers, Jr., FCCP, comments:** Were you prepared for the Centers for Medicare & Medicaid Services adoption of the ICD-10 code set previously scheduled for this October? After several postponements, since issuing the rule in 2009, the use of the ICD-10 code set will be required by CMS starting October 1, 2015, unless it isn’t. The most recent delay, legislated as part of a bill to avoid a 24% cut in physician compensation, stunned the majority of health care providers and payers, including CMS administration. The legislation, *Protecting Access to Medicare Act of 2014*, was quickly developed in the wake of the failure of Congress to repeal the SGR-based physician compensation formula. Included in this legislation was a small section stating that the Department of Health & Human Services cannot adopt the ICD-10 code set as the standard until at least Oct. 1, 2015.



The health-care community, including CMS, had collectively spent hundreds of millions of dollars to meet the 2014 deadline for the changeover. For the past 18 months, CMS has been aggressively committing resources to communication and provider education for the transition.

The legislated delay raises many questions: Will Oct. 1, 2015, actually be the new deadline? If not, how will CMS proceed with implementing the mandated value-based payment system that has been framed around the more precise coding of ICD-10? Work on ICD-10 began in 1983 and was completed in 1992. Will Congress consider legislation that scraps ICD-10 altogether and instead wait for ICD-11 which is due to be released in 2017? And the big question, will there ever be legislation that repeals the current dysfunctional physician compensation formula?

# Business associates’ breach can mean HIPAA trouble for you

BY ALICIA GALLEGOS

Frontline Medical News

CHICAGO – A new HIPAA rule means physicians face broader liability for protected health information breaches by their business associates.

The final omnibus rule on the Health Insurance Portability and Accountability Act broadens the definition of who and what is considered a business associate and places more responsibility on doctors for protected health information (PHI) acts or omissions by such associates.

About “28%-49% of breaches in the health care industry are associated with business associates and how they’re using data,” health law attorney Clinton R. Mikel said at a physicians’ legal issues conference held by the American Bar Association.

“It’s important to know who your business associates are, how you’re [interacting] with them and what they’re doing with your data.”

The final HIPAA omnibus rule went into effect in September 2013, but allowed covered entities

and businesses to continue operating under some existing contracts for up to 1 year. Grandfathered business agreements must be revised to meet the new HIPAA requirements by Sept. 22, 2014.

Under the omnibus rule, a business associate is defined as any person or entity that creates, receives, maintains, or transmits PHI on behalf of a covered entity. The regulation means that business associates now include patient safety organizations, data transmission organizations, personal health record vendors, entities that transmit and need routine access to PHI, and data storage vendors – paper based and cloud based.

On physicians’ immediate checklist of things to be reviewed and updated is their existing business-associate agreement template, said Mr. Mikel, a partner at The Health Law Partners, PC, in Southfield, Mich. The revised agreement should ensure that associates comply with all measures of the Security Rule for electronic PHI and that business associates report any breach of unsecured PHI.

In addition, business associates should enter into contracts only with subcontractors that com-

ply with such agreements and restrict subcontractors from disclosing PHI in an inappropriate manner.

Distribute the new template as soon as possible for all new contracts and evaluate outstanding business associate relationships, Mr. Mikel advised.

Proper data security from cloud-based vendors is especially important in light of the new HIPAA rule, said Hemant Pathak, assistant general counsel for Microsoft. Make certain they are told where and how their data are stored in “the cloud” and have clear data maps and geographic boundary information.

Vendors should be “transparent about what their operations are, have a breach procedure, and be willing to share” their policies, Mr. Pathak added. “It should not be something that is obtuse. It should be something that is clear and transparent.”

Under the omnibus rule, both the doctor and vendor are on the hook if PHI is exposed.

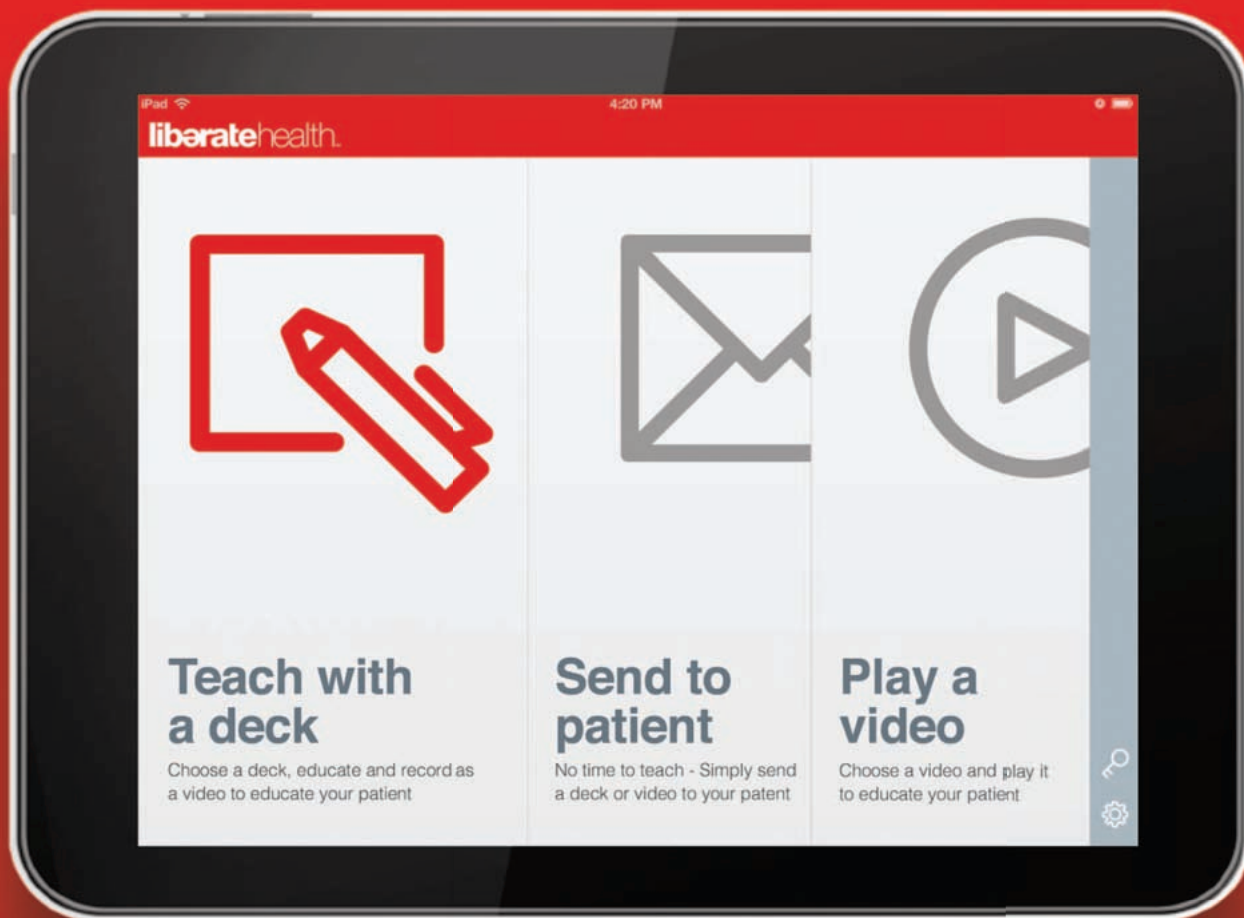
“It’s important for both of us in protecting our reputations and understanding what the needs are from a compliance” standpoint, Mr. Pathak said.



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# Monoclonal antibody attacks new asthma target

BY SHERRY BOSCHERT

*Frontline Medical News*

SAN DIEGO – An investigational human monoclonal antibody suggested a new approach to asthma treatment by showing evidence of anti-inflammatory activity and partial attenuation of early and late asthmatic responses in a proof-of-concept study of 31 patients with mild asthma.

Patients were randomized to intravenous treatment with AMG 157 or placebo for up to 3 months before undergoing allergen-induced challenge and testing. AMG 157 binds human thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine that might be important in initiating allergic inflammation, and prevents receptor interaction.

By day 84, the maximum percentage decrease in the forced expiratory volume at 1 second (FEV<sub>1</sub>) during

late asthmatic response (3-7 hours after allergy challenge) was 46% smaller in the treatment group, vs.

placebo, a significant difference, Gail M. Gauvreau, Ph.D., and her associates reported at an international conference of the American Thoracic Society.

Among secondary outcomes, the area under the curve (AUC) of the time-adjusted percent decrease in FEV<sub>1</sub> during the early asthmatic response was significantly smaller in the treatment group than the control group on day 84. Patients who got AMG 157 showed significantly lower levels of blood and sputum eosinophils before and after allergy challenge and in the fraction of exhaled nitric oxide.

Adverse events were reported in 15 patients on AMG 157 and 12 patients on placebo. No serious adverse events were seen, reported Dr.

Gauvreau of the Firestone Institute of Respiratory Health at McMaster University, Hamilton, Ont.

The study was published online by the *New England Journal of Medicine* (2014 May 20 [doi: 10.1056/NEJMoa1402895]). “This proof-of-concept study suggests that TSLP is a pivotal cytokine not only in allergen-induced airway responses but also in persistent airway inflammation in patients with allergic asthma,” the investigators wrote.

The company that is developing AMG 157 has started a phase II clinical trial, Dr. Gauvreau said in an interview at the meeting.

The population of mild asthmatics in the proof-of-concept study is not the kind of patient who might use this treatment, she said, but this potential treatment pathway offers hope for a new therapy for patients with steroid-resistant asthma.

## VIEW ON THE NEWS

**Dr. Eric Gartman, FCCP, comments:** For our most difficult-to-control asthma patients, we are longing for an effective and more directed alternative to systemic corticosteroids. While this agent has yet to be studied in the appropriate population, any advancement in the science of developing therapies against novel targets in asthma is a needed step in the right direction.

Amgen, which is developing AMG 157, funded the study and analyzed the data. Many of the researchers reported financial associations with Amgen and other companies.

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# Pembrolizumab posts 6.75-month PFS in stage IV NSCLC

BY PATRICE WENDLING

*Frontline Medical News*

CHICAGO – Monotherapy with the experimental anti-PD-1 antibody pembrolizumab induced durable treatment responses and improved progression-free survival in previously untreated stage IV non-small cell lung cancer in an ongoing phase Ib trial.

The overall response rate was 26% (11 of 42 patients) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and 47% (21 of 45 patients) by investigator-assessed, immune-related response criteria (irRC).

Responses are ongoing in 100% of responders by RECIST and 90% of responders by irRC, with the median duration of response not reached after a median of 36 weeks' follow-up, Dr. Naiyer Rizvi said at the annual meeting of the American Society of Clinical Oncology.

Responses in the phase I KEYNOTE-001 study are very comparable with response rates of 15%-32% achieved with classic chemotherapy in the first-line setting in phase III studies using gemcitabine plus cisplatin, taxol plus carboplatin, or pemetrexed plus cisplatin, said invited discussant Dr. Julie Brahmer of Johns Hopkins University, Baltimore.

“The key thing [with pembrolizumab] is that these responses are very long lasting,” she said.

Moreover, median progression-free survival (PFS) with the classic chemotherapy doublets ranged from 4.5 months to 5.3 months but reached 6.75 months by RECIST and 9.25 months by irRC in the interim analysis of pembrolizumab.

“A very early but interesting progression-free survival of 6.75 months is quite intriguing,” Dr. Brahmer said.

Enrollment is expected to begin this September in the phase III KEYNOTE-024 study comparing

pembrolizumab monotherapy with platinum-based doublet chemotherapy in treatment-naive PD-L1 positive, metastatic non-small cell lung cancer (NSCLC), said Dr. Rizvi, a medical oncologist with Memorial Sloan Kettering Cancer Center in New York.

## Study details

Pembrolizumab, previously known as MK-3475, exerts dual ligand (PD-L1 and PD-L2) blockade of the programmed death 1 (PD-1) pathway. It is being investigated in more than 30 different cancers, and it made waves at the ASCO meeting for its

treatment of metastatic melanoma.

Dr. Brahmer said that the key questions for the current study are whether PD-L1 sensitivity was the right biomarker to use and what the best cut-off is.

The KEYNOTE-001 study (clinicaltrials.gov/show/NCT01295827) enrolled 84 previously untreated patients with stage IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0-1. Tumors were classified as PD-L1 positive in 57 patients, using a cut point of at least 1% of tumor cells stained, as measured using a prototype immunohistochemistry assay.

Of these 57 patients, 45 with evaluable imaging at baseline were randomly assigned to pembrolizumab 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Most patients (76%) had non-squamous histology, and 69% were former smokers.

Tumor shrinkage by RECIST criteria occurred in 80% of patients with measurable disease and at least one postbaseline scan, Dr. Rizvi said. Activity was observed across dose levels and across the 2- and 3-week schedules.

Safety data indicate the regimen is “safe and well tolerated,” Dr. Rizvi said.

Nine patients with new tumors would have been considered as having progressive disease and likely taken off therapy if they had been assessed by traditional RECIST criteria rather than irRC, “illustrating that RECIST may not be the best imaging modality to assess patients treated with immunotherapy,” he said.

The study was supported by Merck. Dr. Rizvi reported a consultant or advisory role with Bristol-Myers Squibb and honoraria from Bristol-Myers Squibb, MedImmune, and Roche/Genentech.

## VIEW ON THE NEWS

**Dr. Lary Robinson, FCCP, comments:** In this dose-escalation phase Ib safety trial of pembrolizumab used alone in 45 stage IV NSCLC treatment-naive patients whose tumor expresses PD-L1, there was an intriguing 26%-47% response with a 6.75- to 9.25-month median progression-free survival (depending on response criteria used) with only mild toxicity, which is far better than the classic doublet chemotherapy response.

Further trials of these agents should prove whether this novel immunotherapy approach to systemic treatment of lung cancer is potentially a breakthrough in treatment, that soon may become the preferred first-line, well-tolerated therapy for this very large group of metastatic lung cancer patients who express high levels of PD-L1.



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# PALLIATIVELY SPEAKING: Why consults don't happen

BY DR. STEPHEN J. BEKANICH AND DR. LEIGH A. FREDHOLM

Today our team saw an 89-year-old gentleman with dementia, heart

failure, atrial fibrillation, chronic kidney disease, and problems falling. His last known fall was less than 3 months ago and resulted in a broken hip requiring surgical intervention. This was his fourth hospitalization in

6 months, yet it was the first time he was seen by our service.

The frequency at which physicians order palliative care consults in a particular hospital varies widely. Some reasons for this are not easy fixes –

PC is not available in each hospital (as was the case in two of this gentleman's four hospitalizations), many PC teams are available only Monday-Friday, and patient volumes within a hospital ebb and flow with much less predictability than the tides.

However, some of the reasons

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DR. BEKANICH

DR. FREDHOLM

are amenable to change. These might include the particular group of hospitalists, or one attending physician, utilizing PC consults less frequently than another. Or it may simply be that the connection was not made between the patient's experience and the usefulness of an early PC consults. Screening tools are one method of

**While inquiries on the presence of 'palliative care-related problems' might require more thought or investigation into a patient's situation, we find them to be more fruitful than using diagnosis alone.**

decreasing variability in PC involvement as well as increasing the appropriateness of our service for a particular patient.

There are quite a few palliative care screening tools available. Many of them focus on what most of us would expect, which are the most common diagnoses we see (late-stage cancer, heart failure, cirrhosis, end-stage renal disease, dementia, etc.). Multiple studies have estimated that mature PC programs in large hospitals are consulted on 1%-2% of live discharges. However, we estimate that more than 10% of these discharged patients have palliative needs that go unmet. While it is true that we wish PC could be involved in all of these lives, this large number of people who spend time in the hospital with these diagnoses, coupled with a national shortage of PC providers, translates into an unbalanced equation.

Rather than looking at a specific di-

*Continued on following page*



VIEW ON THE NEWS

**Dr. Jennifer Cox, FCCP, comments:** Palliative care consults are a valuable, yet underutilized service. Palliative care programs, whether just beginning or well established, should place an emphasis on education of clinicians to the broad range of services they can provide. It's not just for hospice anymore.



are overwhelmed on a particular day, leaving the occasional patient who meets criteria unseen. If the consult is urgent, a phone call is appropriate so that an assumption isn't made that the screening tool will catch 100% of the patients.

► **Track data:** When using these tools, palliative care teams have been

able to show things such as improved Hospital Consumer Assessment of Healthcare Providers and Systems survey results and decreased readmissions. Demonstrate what you're doing for your institution so that you can expand the units or patients served.

PC screening tools are an effective way to decrease variability and improve

quality. For examples of tools that we use, please get in touch. Find our contact info and read earlier columns at [ehospitalistnews/Palliatively](http://ehospitalistnews/Palliatively).

*Dr. Bekanich and Dr. Fredholm are codirectors of Seton Palliative Care, part of the University of Texas Southwestern Residency Programs in Austin.*

Continued from previous page

agnosis, we suggest incorporating inquiries on the presence of "palliative care-related problems." While these might require more thought or investigation into a patient's situation, we find them to be more fruitful than using diagnosis alone.

Some examples? Mismatch between the expectations of the medical team vs. patient/family when it comes to prognosis or the goals of care would be one of them. Another might be persistent uncontrolled symptoms despite usual medical management. Family members disagreeing or demonstrating concerns about the goals of care is still another.

Having used various screening tools in multiple hospitals and clinical settings, we suggest the following considerations in setting up your own:

► **Stakeholder management:** The right services and staff need to agree on this being a way to improve quality of care (we always provide an "opt-out" option for those who don't want us involved for some reason).

► **Start small:** Implement screening tools on one unit at a time, or limit the diagnoses to one or two conditions only. You can make the criteria less stringent if the PC team's bandwidth is not too narrow.

► **Be flexible:** Even by starting small, there will be times that the PC teams

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### WORKING TOGETHER FOR PATIENTS WITH LUNG CANCER



## Acetaminophen in ICU sepsis

Renoprotection from page 1

counter the harm.

In an earlier observational study, the Vanderbilt team found that detectible CFH is common in ICU sepsis patients, as well as elevated plasma levels of F<sub>2</sub>-isoprostanes, an indicator of oxidative injury. They also observed that CFH was associated with death, and that exposure to acetaminophen seemed to reduce F<sub>2</sub>-isoprostanes levels and improve survival (Crit Care Med. 2013;41:784-90).

The findings prompted the phase II investigation. The team found that the acetaminophen group had lower levels of F<sub>2</sub>-isoprostanes on study day 2 (mean 24.9 pg/mL vs. 41.2 pg/mL) and lower levels of serum creatinine on study day 3 (mean 1.0 mg/dL vs. 1.3 mg/dL). These differences were

significant and the renal benefit persisted throughout hospitalization.

Acetaminophen patients overall started with a lower mean baseline creatinine level (1.63 mg/dL vs. 2.06 mg/dL), so the investigators reran their analysis, excluding patients on renal replacement therapy. “The baseline imbalance went away, and the story remained the same: There was still a significant decrease in serum creatinine in the acetaminophen group,” said lead investigator Dr. David Janz, a critical care fellow at Vanderbilt.

Despite a favorable trend, acetaminophen did not significantly improve survival, a secondary outcome; one (5.6%) acetaminophen and four (18.2%) placebo patients died.

### VIEW ON THE NEWS

**Dr. Eleanor Summerhill, FCCP, comments:** This small, phase II pilot study suggests that acetaminophen may play a future role in the amelioration of oxidative injury–induced multisystem organ failure. However, clearly more research is necessary.

The study was small, so despite randomization, there were differences in the two treatment groups in regard to age and baseline creatinine levels (the latter corrected for in a secondary analysis). In addition, the effect on oxidative injury markers was not robust beyond day 2. Fi-

nally, the study was underpowered for important outcomes such as hospital length of stay and mortality.

The current study adds to the previous literature demonstrating that acetaminophen inhibits hemoprotein-mediated lipid peroxidation in vitro and in animal models. It also builds upon a previous observational study showing that high plasma cell-free hemoglobin concentrations were associated with poor outcomes in sepsis, and that acetaminophen decreased serum markers of oxidative stress as well as mortality.

Still, the results are strong enough to suggest that acetaminophen might one day prove to be “a potent intervention to improve sepsis outcomes. Even small creatinine changes are as-

sociated with increased length of stay and mortality,” Dr. Janz said.

“Our trial contains some negative results” – most notably no significant  
*Continued on following page*

## Viral reactivation common in septic patients

BY ELIZABETH MECHCATIE

Frontline Medical News

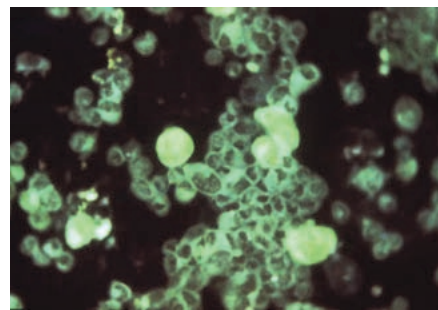
**C**ritically ill patients with sepsis have a much higher prevalence of different viruses than do nonseptic critically ill patients and healthy controls, judging from the findings of a study of more than 800 patients.

These findings provide evidence that the reactivation of latent viruses “is extremely common in patients with prolonged sepsis and is consistent with development of immunosuppression,” researchers concluded.

For some of the viruses, the levels detected in septic patients were comparable to the levels in organ transplant recipients, “who are pharmacologically immunosuppressed, providing further support that our findings are indicative of clinically relevant immunosuppression,” Dr. Anthony Walton, of the department of anesthesiology, Washington University, St. Louis, and his coauthors wrote. The study was published in PLoS One (2014;9:e98819 [doi: 10.1371/journal.pone.0098819]).

In what they said is the first study to evaluate the effect of sepsis on “multiple families of viruses,” the investigators addressed whether sepsis progresses from a hyperinflammatory phase early in the course of sepsis to an immunosuppressive state, a “controversial hypothesis” for explaining the course of sepsis, they wrote.

The researchers compared levels of viruses that included cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), human her-



CDC/DR. CRAIG LYERLA

**Cytomegalovirus levels were elevated in 24.2% of the septic patients.**

pesvirus 6 (HHV-6), and the anellovirus TTV in whole blood and plasma of 560 critically ill patients with sepsis and 161 critically ill patients who did not have sepsis, who were not immunocompromised at baseline; and 164 healthy, age-matched controls, who were ambulatory and whose blood sample was obtained before elective surgery. The median age of the patients was 63-64 years; the median APACHE II score was 18 in the septic group and 5 in the critically ill, nonseptic group; and the median length of stay in the ICU was 11 days and 2 days, respectively; mortality was 26% and 6%, respectively.

Among the key findings:

► CMV seropositivity was detected in about 70% of the patients in the three groups, indicating they had been infected previously. Among these patients, CMV levels were markedly elevated in 24.2% of the septic patients, compared with 1.1% of the critically ill, nonseptic patients and none of the healthy controls.

► EBV was detected in 53.2% of septic patients, vs. 12.1% of the critically

ill, nonseptic patients and 3.6% of the healthy controls.

► HSV was detected in 14.1% of septic patients, vs. 1.5% of the critically ill, nonseptic patients and none of the controls.

► HHV-6 was detected in 10.4% of septic patients, vs. less than 1% of the critically ill, nonseptic patients and 3.3% of the healthy controls.

► TTV was detected in almost 78% of the septic patients, close to 64% of the critically ill, nonseptic patients, and 60.1% of the controls, but levels were lower among the latter two groups.

The authors said that it is “likely that viral detection in the setting of sepsis is not due to primary infection but rather to viral reactivation.” Almost 43% of those with sepsis had

evidence of at least two viruses, which, combined with the “magnitude of viral loads ... provides strong evidence that host immunity is impaired in sepsis,” they added.

Among their other findings was that in the septic patients, the detection rate of the viruses increased for all the viruses with increasing number of days spent in the ICU, and septic patients who had CMV detected in the plasma had significantly higher 90-day mortality than did septic patients with no CMV detected.

The study was funded by the National Institutes of Health. One author is an employee of Biomérieux, which is performing related research.

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### VIEW ON THE NEWS

**Dr. Steven Q. Simpson, FCCP, comments:** The investigators have demonstrated that reactivation of latent viral infections may well contribute to the death of critically ill septic patients. Some of the viral reactivations were associated with secondary fungal infection as well.

Although viral DNA was detected as early as 1 day into sepsis, the bulk of the manifested reactivations occurred over the subsequent 2 weeks. Viral reactivation is a clear marker that the “late” immune suppression of sepsis is a real phenom-



enon and leads to real sequelae.

Nevertheless, it is not yet clear exactly how this information will become useful in practice, as the cost of daily DNA screening for multiple viruses would be prohibitive, unless high-volume demand drives pricing down. One can see, under that scenario, how viral reactivation could be the signal that immune augmentation therapy is required, and that it might be beneficial. This work is not quite ready for prime time, but it is getting ever closer.



Continued from previous page

effect on day 3 F<sub>2</sub>-isoprostanes levels – but “the consistent reduction in creatinine across a number of different analyses and the biologic plausibility underlying this signal prompt further investigation. We need larger studies that focus on length of stay

and mortality,” he said.

Acetaminophen patients were slightly younger (50 vs. 58 years), but besides that and the baseline creatinine difference, the groups were well matched. Both had mean Apache II scores in the low 20s. Nine acetaminophen patients (50%) and seven placebo patients (32%) were intubated.

Both groups received a median of 12 study doses. There was no statistical between-group difference in the number of patients whose AST/ALT topped 400 U/L, a stop-point hit by two acetaminophen patients and one placebo patient. No one in the acetaminophen group developed a rash.

Patients who had liver disease or

who had gotten acetaminophen within 48 hours were among those excluded from the study.

The work was funded by the National Institutes of Health and the American Heart Association. Dr. Janz had no disclosures.

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#### ADEMPAS (riociguat) tablets, for oral use Initial U.S. Approval: 2013

##### BRIEF SUMMARY of PRESCRIBING INFORMATION

For additional information, please see the full Prescribing Information at [www.adempas-us.com](http://www.adempas-us.com).

##### WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning

- Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)
- Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)
- For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).

#### 1 INDICATIONS AND USAGE

##### 1.1 Chronic-Thromboembolic Pulmonary Hypertension

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

##### 1.2 Pulmonary Arterial Hypertension

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

#### 4 CONTRAINDICATIONS

##### 4.1 Pregnancy

Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

##### 4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

##### 4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Embryo-Fetal Toxicity

Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program [see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)].

##### 5.2 Adempas REMS Program

Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program [see Warnings and Precautions (5.1)].

Important requirements of the Adempas 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 Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at [www.AdempasREMS.com](http://www.AdempasREMS.com) or 1-855-4 ADEMPAS.

##### 5.3 Hypotension

Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular

outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]. Consider a dose reduction if patient develops signs or symptoms of hypotension.

##### 5.4 Bleeding

In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

##### 5.5 Pulmonary Veno-Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

#### 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
- Hypotension [see Warnings and Precautions (5.3)]
- Bleeding [see Warnings and Precautions (5.4)]

##### 6.1 Clinical Trials Experience

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

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years [See Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

**Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)**

Adverse Reactions	Adempas % (n=490)	Placebo % (n=214)
Headache	27	18
Dyspepsia and Gastritis	21	8
Dizziness	20	13
Nausea	14	11
Diarrhea	12	8
Hypotension	10	4
Vomiting	10	7
Anemia (including laboratory parameters)	7	2
Gastroesophageal reflux disease	5	2
Constipation	5	1

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

#### 7 DRUG INTERACTIONS

##### 7.1 Pharmacodynamic Interactions with Adempas

**Nitrates:** Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].

**PDE Inhibitors:** Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see Contraindications (4.3) and Clinical Pharmacology (12.2)]. Clinical experience with co-administration of Adempas and

# ACIP: Live attenuated intranasal flu vaccine is best

BY MICHELE G. SULLIVAN  
*Frontline Medical News*

The live attenuated intranasal flu vaccine is the preferred method of immunizing healthy children

aged 2-8 years against seasonal influenza, a federal panel has recommended.

At a meeting of the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, committee members unan-

imously agreed that healthy children with no contraindications should receive the quadrivalent live attenuated intranasal vaccine (LAIV) rather than an inactivated intranasal vaccine (IIV), provided that the LAIV is readi-

ly available. "Vaccination should not be delayed in order to procure LAIV," the recommendation reads.

The committee approved the recommendation after hearing an evidence review that found the LAIV to be "moderately" more effective for this age group than the IIV was. Although the data are not plentiful, they suggest that it would probably prevent about 47 more lab-confirmed cases of flu per 1,000 children than the IIV, said Dr. Lisa Grohskopf, a medical officer in the influenza division of the CDC.

However, Dr. Grohskopf said, she and her colleagues didn't feel that the studies were strong enough to make any initial recommendations to the committee about whether the LAIV could safely be used in children with a history of wheezing or asthma. The studies didn't drill down into data on this group enough, and the data are now too old to be completely reliable for this population.

Asthma and wheezing are not strict contraindications to the LAIV, she said, but ACIP does not recommend it for children with those issues or for those with any chronic conditions that might predispose them to complications from the flu.

Dr. Grohskopf's review was based on two studies – one published in 2006 and one in 2007. The earlier study was an open-label trial that randomized about 2,300 children aged 6-71 months to either the LAIV or an IIV. The much larger 2007 study randomized about 16,000 children aged 6-59 months to the two vaccine types or to matching placebos.

The pooled analysis was limited to healthy children aged 24-59 months who were without a history of asthma or wheezing. The primary endpoint of lab-confirmed influenza infection was significantly less likely among children who had received the LAIV (hazard ratio, 0.47). The secondary endpoint of influenza-associated otitis media was also significantly less likely to occur among those who got the LAIV (HR, 0.47).

She also examined these same endpoints in children who had a history of wheezing or asthma. The LAIV significantly reduced the risk of lab-confirmed influenza in this group (HR, 0.53). There were no significantly increased risks of medically significant wheezing in the children, regardless of whether or not they had experienced wheezing within the past 12 months.

other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

## 7.2 Pharmacokinetic Interactions with Adempas

**Smoking:** Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who stop smoking [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

**Strong CYP and P-gp/BCRP inhibitors:** Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see *Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*].

**Strong CYP3A inducers:** Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see *Clinical Pharmacology (12.3)*].

**Antacids:** Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see *Clinical Pharmacology (12.3)*].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category X

##### Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see *Boxed Warning and Contraindications (4.1)*].

##### Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and humans. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

### 8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

### 8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see *Nonclinical Toxicology (13.2)*].

### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see *Clinical Studies (14)*]. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see *Clinical Pharmacology (12.3)*].

### 8.6 Females and Males of Reproductive Potential

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with

Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see *Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)*].

**Contraception:** Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. 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*].

### 8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see *Clinical Pharmacology (12.3)*].

### 8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

## 17 PATIENT COUNSELING INFORMATION

### See FDA-approved patient labeling (Medication Guide).

#### Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*]. Instruct females of reproductive potential to use effective contraception and to contact her physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

#### Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see *Warnings and Precautions (5.2)*]. Male patients are not enrolled in the Adempas REMS Program. Inform female patients (and their guardians, if applicable) of the following important requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.6)*].
- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

#### Other Risks Associated with Adempas

- Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
- Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
- Instruct patients on the dosing, titration, and maintenance of Adempas.
- Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
- Advise patients that antacids should not be taken within 1 hour of taking Adempas.
- Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see *Adverse Reactions (6.1)*]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

Manufactured for:



**Bayer HealthCare**

Bayer HealthCare Pharmaceuticals Inc.  
Whippany, NJ 07981

Manufactured in Germany

Issued May 2014

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# Focusing on pediatrics: New initiatives from CHEST

BY DR. MARY  
CATALETTO, FCCP, FAAP

This year, the American College of Chest Physicians (CHEST) is proud to announce some new initiatives focusing on important issues in respiratory health and disease in infants, children, and adolescents. As treatment advances allow longer and better survival in children born prematurely, with neuromuscular diseases and many other respiratory diseases and dysfunction, pediatric pulmonologists are looking for additional resources to stay up to date on the most recent advances and technologies available within our field.

To address this need, *CHEST™ SEEK Pediatric Pulmonary Medicine: First Edition* is now available for preorder. SEEK features multiple choice questions consisting of patient cases and clinical vignettes developed by experts in the fields of pediatric pulmonology, pediatric chest imaging, pathology and laboratory science, sleep medicine, and pediatric critical care. SEEK is loosely aligned with the American Board of Pediatrics blueprint on pediatric pulmonology, providing questions in each of the major content areas including Clinical Diseases, Evaluation/Diagnosis, Prevention/Therapy, Lung Growth and Development, Physiology, Cell Biology, and Lung



Defenses. Postgraduate fellows and practitioners alike will find SEEK useful for board preparation and for use in conjunction with all CHEST pediatric offerings.

Celebration of Pediatric Pulmonology is another exciting offering. As a collaboration between the American Academy of Pediatrics and CHEST, Celebration is offered on alternating years as the Pediatric Pulmonary Medicine Board Review course. While the board review focuses on content likely to appear on the board exam, Celebration identifies hot topics, new guidelines, and practice gaps relevant for practitioners responsible for the health, evaluation, and care of children with respiratory illnesses. Each program is designed to complement and enhance your experience and training within the field of pediatric pulmonary medicine.

CHEST has also acquired a variety of low-fidelity pediatric simulation task trainers, which will further enhance pediatric live-learning courses. In addition to the task trainers, CHEST is working with a variety of industry providers to acquire a series of high-fidelity simulation tools for future pediatric courses held in the new CHEST Innovation, Simulation, and Training Center, equipped with six live-learning suites and eight additional breakout rooms.

# CHEST Foundation offers education material for patients

Do you know about the updated patient education materials available on the CHEST website? Resources can be accessed under the Patient Education link ([chestnet.org/Foundation](http://chestnet.org/Foundation)) of the Foundation tab. Currently, information on these topics is available:

- ▶ Asthma
- ▶ COPD
- ▶ Cough
- ▶ DVT/blood clots
- ▶ Lung cancer
- ▶ Pulmonary fibrosis
- ▶ Sarcoidosis
- ▶ Sleep apnea

Each topic gives information on symptoms, causes, risk factors, complications, tests and diagnosis, treatment, and drugs, as well as links to other informative sources. Resources include handouts, videos, prevention messaging, and other helpful activities. For example, patients can watch an instructional video on the proper way to use their in-

haler by clicking on a link in the “Other Resources” section of the Asthma and COPD pages ([chestnet.org/Foundation/Patient-Education-Resources/Asthma/Other-Resources](http://chestnet.org/Foundation/Patient-Education-Resources/Asthma/Other-Resources)).

The CHEST Foundation’s Patient Education Resources empower your patients to take care of their health. Resources are being continually expanded and updated. Check back often for new materials.

Patient Education materials are made possible through funding from The CHEST Foundation and its generous corporate supporters: Forest Pharmaceuticals, Genentech, Pfizer, Sunovion, and Janssen. Contributions to The CHEST Foundation help support this important resource.

Make a donation today at [chestnet.org/Foundation](http://chestnet.org/Foundation) or contact Patti Steele, Annual Fund Manager, at 224/521-9527.

# Austin: Come for the day or make a weekend of it

If you’d like to attend CHEST 2014 but have trouble scheduling time away from your practice, consider the 1-day registration. Register for any given day, Sunday through Thursday. Or, attend for the weekend by registering for a postgraduate course on Saturday and one day on Sunday. If you come for the weekend, consider bringing your family. You won’t be alone—there’s so much to do for everyone in Austin.

## Postgraduate courses

**Saturday, October 25**

Start your meeting by attending a postgraduate course, focusing on specific topics to offer an intensive learning experience. Additional registration is required.

- ▶ Pulmonary Literature Review
- ▶ Sleep Medicine 2014: An Update

on the Literature and the Use of New Technology to Improve Your Practice

- ▶ Update in Thoracic Imaging
- ▶ Was This Part of My Fellowship? A Case-Based Review of Critical Care Issues for the Real World



## Program highlights

CHEST 2014 is your connection to focused clinical education that will help optimize your patient care. The relevant sessions and community of innovative problem-solvers in attendance will be sure to inspire and energize you and your career. Don’t miss these highlights:

## General sessions

**Sunday, October 26 –  
Thursday, October 30**

Choose from hundreds of sessions, offered in a variety of instructional formats.

## CHEST Simulation Center

**Sunday, October 26 –  
Wednesday, October 29**

Practice your clinical skills in a hands-on learning environment, featuring simulation sessions and SEGs: Simulation Enhanced General Sessions.

## Opening sessions

**Sunday, October 26 –  
Monday, October 27**

Attend to hear keynote speakers Dan Heath, co-author of *Decisive: How to Make Better Choices in Life and Work* (Sunday), and Kevin Pho, founder of [KevinMD.com](http://KevinMD.com) (Monday).

## Clinical Resource Center

**Monday, October 27 –  
Wednesday, October 29**

Don’t miss the showcase of diagnostic and treatment solutions for optimal patient care.

## Explore Austin!

With temperatures averaging in the mid to upper 70s in October, Austin visitors will enjoy the sunshine and moderate climate. Explore Austin’s parks, enjoy some live music, savor Austin’s specialty – barbeque, or visit the University of Texas. Find out about Austin’s unique charm at [austintexas.org](http://austintexas.org), or check out our Austin Pinterest board at [pinterest.com/acpcchest](http://pinterest.com/acpcchest).

## Register early and save

Learn more about CHEST 2014, and register at [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org). Register by August 29 and save up to \$150.



For your patients with chronic obstructive pulmonary disease (COPD) who require maintenance bronchodilator treatment

## Help Your Patients Breathe Better With ANORO ELLIPTA



### Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta<sub>2</sub>-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

### Important Safety Information for ANORO ELLIPTA

#### **WARNING: ASTHMA-RELATED DEATH**

- **Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol.**
- **The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.
- ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (eg, salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.
- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur.
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy.
- Vilanterol can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. If such effects occur, ANORO ELLIPTA may need to be discontinued. ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.



## ANORO ELLIPTA significantly improved trough (predose) FEV<sub>1</sub> by 167 mL vs placebo (*P*<0.001) at Day 169<sup>1</sup>

A 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared the efficacy and safety of ANORO ELLIPTA (n=413) and placebo (n=280), each administered once daily by the ELLIPTA inhaler. The primary endpoint was trough (predose) FEV<sub>1</sub> at Day 169 (defined as the mean of the FEV<sub>1</sub> values obtained 23 and 24 hours after dosing on Day 168).<sup>1</sup>

### Once-daily ANORO ELLIPTA

The first and only FDA-approved product for patients with COPD combining 2 long-acting bronchodilators in 1 inhaler



### Important Safety Information for ANORO ELLIPTA (cont'd)

#### WARNINGS AND PRECAUTIONS (cont'd)

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

#### ADVERSE REACTIONS

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

#### DRUG INTERACTIONS

- Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic exposure to vilanterol and cardiovascular adverse effects may occur.
- ANORO ELLIPTA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the effect of adrenergic agonists, such as vilanterol, on the cardiovascular system may be potentiated by these agents.
- Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as vilanterol, but may produce severe bronchospasm in patients with COPD.
- Use with caution in patients taking non-potassium-sparing diuretics, as electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists.
- Avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

**Reference: 1.** Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umecclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107(10):1538-1546.

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

ANORO ELLIPTA was developed in collaboration with Theravance



**ANORO**<sup>™</sup> **ELLIPTA**<sup>™</sup>  
(umecclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)

## BRIEF SUMMARY

### ANORO™ ELLIPTA™ (umeclidinium and vilanterol inhalation powder) FOR ORAL INHALATION USE

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

#### WARNING: ASTHMA-RELATED DEATH

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA [see Warnings and Precautions (5.1)].

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

#### 1 INDICATIONS AND USAGE

ANORO ELLIPTA is a combination anticholinergic/long-acting beta<sub>2</sub>-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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

#### 4 CONTRAINDICATIONS

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

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Asthma-Related Death

- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

##### 5.2 Deterioration of Disease and Acute Episodes

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

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta<sub>2</sub>-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta<sub>2</sub>-agonist becomes less effective; or the patient needs more short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

##### 5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta<sub>2</sub>-Agonists

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

##### 5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors

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

##### 5.5 Paradoxical Bronchospasm

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

##### 5.6 Hypersensitivity Reactions

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

##### 5.7 Cardiovascular Effects

Vilanterol, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms [see Clinical Pharmacology (12.2) of full Prescribing Information]. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

#### 5.8 Coexisting Conditions

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

#### 5.9 Worsening of Narrow-Angle Glaucoma

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

#### 5.10 Worsening of Urinary Retention

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

#### 5.11 Hypokalemia and Hyperglycemia

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

#### 6 ADVERSE REACTIONS

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

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

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

#### 6.1 Clinical Trials Experience

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

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

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

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

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

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

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

#### 7 DRUG INTERACTIONS

##### 7.1 Inhibitors of Cytochrome P450 3A4

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when



considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleanandomycin, voriconazole) [see *Warnings and Precautions (5.4), Clinical Pharmacology (12.3) of full Prescribing Information*].

#### 7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

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

#### 7.3 Beta-Adrenergic Receptor Blocking Agents

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

#### 7.4 Non-Potassium-Sparing Diuretics

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

#### 7.5 Anticholinergics

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

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

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

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

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

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

#### 8.2 Labor and Delivery

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

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

#### 8.3 Nursing Mothers

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

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

**Vilanterol:** It is not known whether vilanterol is excreted in human breast milk. However, other beta<sub>2</sub>-agonists have been detected in human milk.

#### 8.4 Pediatric Use

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

#### 8.5 Geriatric Use

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

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

#### 8.6 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in C<sub>max</sub> or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls.

Studies in subjects with severe hepatic impairment have not been performed [see *Clinical Pharmacology (12.3) of full Prescribing Information*].

#### 8.7 Renal Impairment

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

### 10 OVERDOSAGE

No case of overdose has been reported with ANORO ELLIPTA.

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

### 10.1 Umeclidinium

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

### 10.2 Vilanterol

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

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

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

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

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

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

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

### 17 PATIENT COUNSELING INFORMATION

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

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

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

Provide patients with such medicine and instruct them in how it should be used.

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

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

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

**Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists:** Instruct patients to not use other medicines containing a LABA.

Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

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

**Risks Associated With Beta-Agonist Therapy:** Inform patients of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

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

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ANORO ELLIPTA was developed in collaboration with Theravance .



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# NETWORKS: Resuscitation techniques, post-polio care, and more

## Critical Care

### ProCESS trial

Early resuscitation with optimization of oxygen delivery ( $Do_2$ ) using central venous saturation ( $Scvo_2$ ) or lactate clearance (Rivers et al. *N Engl J Med.* 2001;345[19]:1368; Jones et al. *JAMA.* 2010;303[8]:739) improved survival compared with standard resuscitation in established severe sepsis (Hayes et al. *N Engl J Med.* 1994;330[24]:1717; Gattinoni et al. *N Engl J Med.* 1995;333[16]:1025).

The ProCESS trial brought us some new data revealing no differences in mortality using different resuscitation techniques: (1) early goal-directed therapy (EGDT) with a protocol of targeted  $Scvo_2$  with a central venous catheter (similar to Rivers et al); (2) an alternative protocolized approach based on lactate clearance; (3) a nonprotocolized approach based on "clinical judgment" (*N Engl J Med.* 2014;370[18]:1683).

The EGDT group had a higher percentage of use of pressors, dobutamine, and transfusion with no difference in the outcome compared with the other groups. The usual care of the participating EDs from university hospitals reached the same outcome without use of a protocol for sepsis treatment. This group performed early intervention in sepsis as in the other groups, possibly because over the last decade, the importance of early resuscitation and antibiotic therapy has been emphasized. Finally, all three groups received similar prandomization treatments with fluids, vasopressors, and early antibiotics. The average  $Scvo_2$  was already normal in the EGDT group at the time of central venous catheterization, supporting that a rapid resuscitation was initiated before randomization in the ED.

Dr. Maximiliano A. Tamae Kakazu  
Steering Committee Member

## Home Care

### Care for post-polio patients

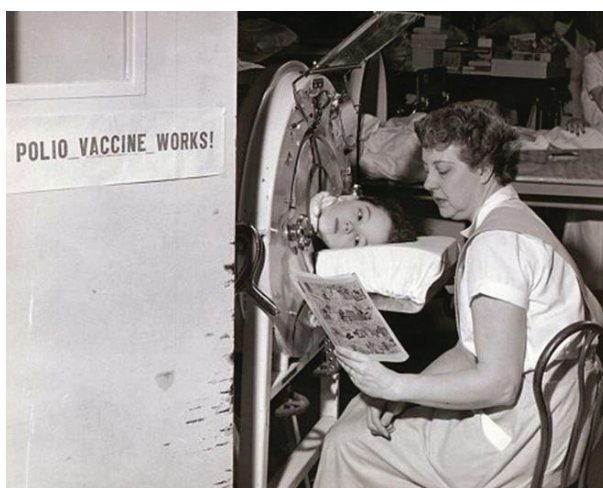
In the early 1950s, 1,500 poliomyelitis patients were in tank respirators (iron

lung) (Daniel and Robbins, eds, *Polio*, University of Rochester Press, 1997). Today, the number is less than a dozen. It is estimated that 575,000 survivors are alive today in the United States (Becker. *Post-Polio Health International*, 2006).

The number who had bulbar or high spinal polio is unknown, but scattered around the country are individuals with increased breathing muscle weakness due to remote acute poliomyelitis. The effects are insidious. Survivors accommodate to feel better. They sleep in an upright position and may resort to home remedies. For example, "I ask my husband to take me for a ride with the windows open." They often are forced to cease activities that cause breathlessness. Ultimately, some are taken to the ED with respiratory failure with no prior intervention.



DR. KAKAZU



Polio survivors, treated with tank respirators in the 1950s, often now find their issues mistaken for apnea.

They and their fellow survivors, some of whom have used ventilation at home since being released from the polio wards in the late 1950s and early 1960s are referred to sleep medicine providers who often misperceive their issues to be obstructive sleep apnea. Patients become extremely frustrated with the health-care system as they struggle to get the appropriate tests, diagnosis, and treatment.

One of the reasons the CHEST Home Care Section began in 1995 was to address the needs of this special aging population and to provide education at the CHEST annual meeting, which includes the Margaret Pfrommer Memorial Lecture in Long-term Mechanical Ventilation.

Join the Home Care NetWork to collaborate with health professionals managing similar patients and to obtain information for your patients from the International Ventilator Users Network ([ventusers.org](http://ventusers.org)) and

Post-Polio Health International ([post-polio.org](http://post-polio.org)).

Joan L. Headley, MS  
Steering Committee Member

## Clinical Research

### Disparities in clinical research

The 2012 national health-care disparities report by the Agency for Healthcare Research and Quality ([ahrq.gov](http://ahrq.gov)) shows that access to clinical research trials is suboptimal, especially for minority and low-income groups, and while overall quality of health care is improving, access is getting worse, and disparities are not changing. This often leads to clinical research that does not assess how treatments may affect members of specific populations differently (Murthy et al. *JAMA.* 2004;291[22]:2720; Ford et al. *Cancer.* 2008;112[2]:228). Participation barriers to clinical trials for minorities include mistrust due to mistreatment faced by groups such as African-Americans in the past, lack of awareness and low literacy, social economic obstacles, lack of insurance, and study design eligibility criteria (Friedman et al. *Am J Health Promot. Am J Health Promot.* 2014 Mar 26. [Epub ahead of print]).

Major steps clinical researchers can take in improving minority enrollment include involving minority community stakeholders in designing clinical trials and communicating results and the implications of trials to specific communities after the trial is complete. This can be enhanced by improving cultural competence and communicating effectively across cultures, using lay outreach workers

from the targeted populations, and involving community-based organizations and places of worship, including minority principal investigators and configuring electronic health records to trigger alerts if patient is likely to be eligible for an ongoing trial during clinical encounters. (Lieu et al. *Am J Respir Crit Care Med.* 2011; 184[7]:848; Friedman et al. *Am J*



*Health Promot.* 2014 Mar 26. [Epub ahead of print]).

Dr. Akram Khan, FCCP  
Steering Committee Member

## Interstitial and Diffuse Lung Disease

### Effective therapies for IPF

The much-anticipated results of four major randomized control trials in IPF were reported during the 2014 ATS meeting.

The initial report of the PANTHER-IPF trial demonstrated that combination therapy with prednisone, azathioprine, and n-acetylcysteine (NAC) was harmful (Raghu et al. *N Engl J Med.* 2012; 366[21]:1968). Now, the remaining two-arm PANTHER-IPF (NAC vs placebo) demonstrated that NAC was not better than placebo to preserve FVC (Martinez et al. *N Engl J Med.* 2014; 370[22]:2093).

The INPULSIS trials enrolled 1,066

Continued on page 26

## Useful internet resources

- ▶ Agency for Healthcare Research and Quality: [ahrq.gov](http://ahrq.gov)
- ▶ National Minority Quality Forum: [nmqf.org](http://nmqf.org)
- ▶ Center for Information and Study on Clinical Research Participation: [ciscrp.org](http://ciscrp.org)
- ▶ Office of Minority Health: [minorityhealth.hhs.gov](http://minorityhealth.hhs.gov)
- ▶ NIH National Institute on Minority Health and Health Disparities: [nimhd.nih.gov](http://nimhd.nih.gov)
- ▶ Think Cultural Health: [thinkculturalhealth.hhs.gov](http://thinkculturalhealth.hhs.gov)
- ▶ Ethnomed (cultural beliefs, medical issues and related topics pertinent to the health care of immigrants): [ethnomed.org](http://ethnomed.org)



# This month in *CHEST*: Editor's picks

BY DR. RICHARD S. IRWIN, MASTER FCCP  
*Editor in Chief*

**Decrease in Mortality in Severe Community-Acquired Pneumococcal Pneumonia: Impact of Improving Antibiotic Strategies (2000-2013).**  
*By Dr. S. Gattarello et al.*

**Functional Impact of a Spectrum of Interstitial Lung Abnormalities in Rheumatoid Arthritis.**  
*By Dr. T. J. Doyle et al.*

EDITORIAL  
**CHEST Launches a New Era With a New Design.**  
*By Dr. Richard S. Irwin et al.*

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE  
**Mechanical Ventilatory Support in Potential Lung Donor Patients.**  
*By Dr. R. Bansal et al.*

COMMENTARY  
**Bronchial Thermoplasty: Reappraising the Evidence (or Lack Thereof).**  
*By Dr. V. N. Iyer and Dr. K. G. Lim.*

# July issue showcases new design

**W**elcome to the new look of *CHEST*. In the July issue, the journal introduced a new design matching the new brand of *CHEST*.

The new article pages are designed to present key information, such as abstracts, in a prominent position, making it easier for you to find the information you need. Articles with enhanced content, such as videos, have visual icons both within the Table of Contents and at the top of the article view.

Articles with enhanced content, such as videos, have visual icons both within the Table of Contents and at the top of the article view. *CHEST* has changed the way content is delivered. The popular case-based sections have been moved to online-only publication and have

been curated into a new collection called Online Exclusives. These articles include the following sections: Chest Imaging and Pathology for Clinicians; Selected Reports;

and Pulmonary, Critical Care, and Sleep Pearls. Ultrasound Corner, the other case-based series, has been published as online-only since its launch in January 2013.

Publishing these articles online allows *CHEST* to include enhanced content within them, enriching readers' experience. The articles currently are and will continue to be indexed by PubMed, the Web of Science, and all search engines. *CHEST*'s online-only content can be viewed in a smartphone browser or on iOS devices with the *CHEST* app.

Besides moving our case-based series to online-only, we are also moving our Correspondence section into Online Exclusives. Each letter includes a link to the original article for which it is commenting, along with the response letter from the original authors.

Showcasing these articles as Online Exclusives enables readers to more easily see the referenced and related material, bringing more relevance to these letters.

The Online Exclusives articles will still be included in the print Table of Contents in each issue with their e-page numbers.

Or, if you are not currently receiving our monthly issue alert, you can sign up for it on the *CHEST* website: [journal.publications.chestnet.org](http://journal.publications.chestnet.org).



## 2014 Education Calendar

Pediatric Pulmonary Medicine Board Review  
August 22-25  
Orlando, FL

Critical Care Medicine Board Review  
August 22-25  
Orlando, FL

Pulmonary Medicine Board Review  
August 27-31  
Orlando, FL

CHEST 2014  
October 25-30  
Austin, TX

### BRONCHOSCOPY

**NEW!** Comprehensive Bronchoscopy With Endobronchial Ultrasound  
September 25-27

### MECHANICAL VENTILATION

Essentials of Mechanical Ventilation for Providers  
July 24

Mechanical Ventilation: Advanced Critical Care Management  
July 25-27

### SLEEP

**NEW!** Essentials of Sleep-Disordered Breathing  
July 18

Management of Sleep-Disordered Breathing in Clinical Practice  
July 19-20

### ULTRASONOGRAPHY

Focused Thoracic and Vascular Ultrasound  
September 18-19

Critical Care Echocardiography  
September 20-21

**NEW!** Ultrasound Train-the-Trainer: Program Development for Key Faculty in Pleural and Vascular Ultrasonography  
November 13-14

Ultrasonography: Essentials in Critical Care  
December 3-5

## American College of Chest Physicians Innovation, Simulation, and Training Center



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Continued from page 24

patients who were randomized to nintedanib or placebo. Patients randomized to nintedanib had lower annual rate of decline in FVC compared with placebo (Richeldi et al. *N Engl J Med.* 2014; 370[22]:2071). ASCEND enrolled 555 patients to either pirfenidone or placebo. Patients randomized to pirfenidone were less likely to have a 10% decline in FVC and had better progression-free survival (King et al. *N Engl J Med.* 2014;370[22]:2083). Gastrointestinal side effects were common with both drugs but the overall safety profile was acceptable.

These results mark the beginning of a new era. For the first time, we have drugs that have demonstrated efficacy in well-designed IPF randomized control trials. Moreover, the results of PANTHER-IPF demonstrate unequivocally that the strategy considered to be the standard of care for many years was causing harm. Moving forward, the

need for precise IPF diagnosis must be underscored, as patients with other fibrosing lung diseases were not eligible for these trials. ASCEND and INPULSIS utilized a central review process to determine study eligibility and included only patients with mild to moderate disease, so the effect in advanced cases is not known. Notwithstanding these concerns, we finally have some good news to share with our IPF patients!

Dr. Joao Alberto M. de Andrade, FCCP  
Vice-Chair

### Airways Disorders

#### Bronchoscopic lung volume reduction (BLVR)

Medical therapy for patients with COPD remains frustrating. Surgical lung volume reduction (SLVR) is marred with high morbidity and mortality whereas lung transplantation is available for a few.

The National Emphysema Treatment Trial (NETT) (Fishman et al. *N Engl J Med.* 2003;348 [21]:2059) demonstrated that patients with predominantly upper lobe emphysema and a low exercise tolerance had significantly lower mortality rates, improved exercise capacity, and improved health-related quality of life when treated with lung volume reduction surgery.

The NETT provided a platform for BLVR techniques. Current bronchoscopic treatments can be divided into two main categories: those that promote atelectasis and those that attempt to improve air trapping. Treatments aimed at producing atelectasis can be further subdivided into bronchial occlusion devices and parenchymal injury methods.

The objective of bronchial occlusion is to induce atelectasis of a lung segment or subsegment, thus resulting in decrease or shift of lung volume from areas with poor to better gas exchange. Bronchial occlusion devices include bronchial plugs (Watanabe spigot) and bronchial valves. Parenchymal injury methods target the lung parenchyma and aim to cause atelectasis through direct inflammatory or mechanical injury. These irreversible parenchymal injury methods include: biologic and polymeric sealants (Criner et al. *Am J Respir Crit Care Med.* 2009;[1]:791), thermal vapor ablation (Snell et al. *Ann Thorac Surg.* 2009;[86]:1993),

and endobronchial coils (Herth et al. *Thorax.* 2010;[68]:225).

The airway bypass method attempts to improve hyperinflation by creating additional transbronchial passages for air to escape. This technique failed to show benefit. Most of the other modalities are undergoing clinical investigations in the United States; some are approved in Europe.

BLVR carries a great deal of promise. It appears better tolerated than surgical LVRS. Optimization of both procedural techniques and patient selection could make this an attractive option for many patients with COPD.

Dr. Ali I. Musani, FCCP  
Steering Committee Member



DR. DE ANDRADE



DR. MUSANI

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> Register Now [chestmeeting.chestnet.org](http://chestmeeting.chestnet.org)



# SLEEP STRATEGIES: Choosing the right CPAP equipment

BY DR. MATTHEW R. EBBEN AND DR. ANA C. KRIEGER, FCCP, FAASM

Continuous positive airway pressure (CPAP) has long been considered the gold standard treatment for OSA. Recently, a variety of new treatment approaches have become available for mild and moderate OSA, including nasal resistance valves, nerve stimulators, and negative pressure devices. Nonetheless, CPAP remains unmatched in efficacy, as well as the frequency and severity of side effects associated with treatment. The main drawback of CPAP is the required use of a mask interface and pressurized air during sleep, which is uncomfortable for some patients.

This article will highlight recent work investigating issues associated with equipment choice for practitioners treating OSA patients with CPAP and discuss how proper equipment choices and educational programs can reduce common complaints associated with CPAP use.

## Mask choice

Finding a suitable mask interface is one of the most critical aspects of achieving adequate treatment compliance. The four general styles to choose from are oronasal (full-mask), standard nasal (over the nose), nasal pillows (in the nose), and the rarely-used oral.

Most clinicians choose an initial mask after CPAP titration based on a combination of patient feedback and air leakage rates but may change the mask style after home implementation in order to improve patient tolerance. Unfortunately, many clinicians are unaware that CPAP levels may need to be adjusted after changing masks. Two studies have shown that oronasal masks require significantly more pressure to ensure adequate OSA treatment during CPAP titration compared with standard nasal and nasal pillows masks (Ebben et al. *Sleep Med.* 2012;13[6]:645; Borel et al. *PLoS ONE.* 2013;8[5]:e64382).

In a separate study in which nasal masks were replaced with oronasal masks, the apnea-hypopnea index (AHI) increased to greater than 10 events per hour in half of patients who had been previously titrated to less

than five per hour with the nasal mask (Ebben et al. *Sleep Med.* 2014;15[6]:619). Caution should be used when making a mask change to ensure that adequate disease control is maintained.

## Humidification

In the past few years, humidification has been routinely added to most CPAP machines in order to improve comfort. The benefit appears to come from a reduction in dryness related to regular CPAP use (Ruhle et al. *Sleep Breath.* 2011;15[3]:479). Some patients report that humidification is particularly helpful in the winter months, when indoor humidity is low. Heated humidification has been found to produce significantly more humidity and causes less insensible water loss from the respiratory tract compared with unheated units (Randerath et al. *Eur J Respir.* 2002;20[1]:183). Unfortunately, the humidifier significantly increases the size and weight of the treatment machine, though it can be removed for travel if desired. In addition, the humidifier requires additional maintenance; if not cleaned regularly, there is a risk of bacterial colonization of the humidification chamber (Chin et al. *J Clin Sleep Med.* 2013;9[8]:747).

In some instances, patients may complain of excess water condensation in the hose, particularly in the presence of a cool sleeping environment. Some CPAP manufacturers now offer heated hoses, which can significantly reduce this condensation. A second option is to add an insulating hose cover to help maintain a higher internal temperature. Generally, these covers are a good choice if the cost of a heated hose is not covered by a patient's insurance.

Some patients may complain of excess water condensation in the hose, particularly in the presence of a cool sleeping environment. Some CPAP manufacturers now offer heated hoses, which can significantly reduce this condensation. A second option is to add an insulating hose cover to help maintain a higher internal temperature. Generally, these covers are a good choice if the cost of a heated hose is not covered by a patient's insurance.

## Pressure relief

A common complaint often heard from patients using CPAP is that the pressure feels too high, particularly when exhaling. In response, some equipment makers have developed pressure relief systems that allow an adjustable pressure drop during exhalation with standard CPAP units. These systems work by transiently reducing pressure during exhalation by a set amount, according to their proprietary algorithm (Dolan et al. *Sleep and Breath.* 2009;13:73). However, not

## EDITOR'S COMMENT

The provision of positive airway pressure therapy to patients with sleep-disordered breathing is a daily practice for sleep medicine providers. Though the suboptimal adherence data are long-known and well-published, are there opportunities for us to help our patients do better? Has the limited time we allow in our clinic schedules for a routine sleep apnea follow-up impaired our patients' ability to master the art of using CPAP? Drs. Ebben and Krieger use this



month's Sleep Strategies to review important considerations of which providers should remain mindful when prescribing and monitoring this treatment. Recognizing that CPAP is a difficult therapy to reliably use is an important part of being a sleep medicine provider. Partnering with our patients to improve their acceptance and long-term use of this vitally important intervention is an underemphasized, but no less critical, part of the job.  
Dr. David Schulman, FCCP  
Section Editor

all patients find this pressure relief effective at making CPAP easier to use. When tested empirically, pressure relief has not been consistently shown to improve CPAP compliance (Dolan et al. *Sleep Breath.* 2009;13[1]:73).

## Compliance data monitoring

Many patients benefit from discussing and reviewing treatment efficacy at

their follow-up visits. Most modern CPAP equipment allows for such data monitoring, that may include duration and specific times of machine use, leak rate, snoring periods, and residual respiratory events, subdivided into hypopneas and apneas. In some cases, the software can distinguish between central ("clear air-

*Continued on following page*

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Continued from previous page

way”) and obstructive events using forced oscillation techniques to measure upper airway resistance. This information allows the clinician to adjust settings and ensure that treatment is optimized and used as prescribed.

Clinicians should familiarize them-

selves with the different reporting systems that provide these data, and train their office staff on using software to capture information for all CPAP users. Notably, the algorithms used to capture residual respiratory events are not completely accurate; identification of such events is based only on measures of flow.

While it is probably acceptable to take extreme values at face value, whether low or very high, the imprecision of the methodology makes it more difficult to reliably use middling values in a clinical setting. (Schwab et al. *Am J Respir Crit Care Med*. 2013;188[5]:613). If a patient remains symptomatic despite no evidence of

residual respiratory events from the adherence data download, a reiteration study should still be considered.

### Educational programs

Adherence to CPAP has been shown to increase when providers engage patients in educational programs to enhance compliance and understanding of the potential health-care consequences of untreated OSA (Lai et al. *Chest*. 2014 May 8. doi: 10.1378/chest.13-2228. [Epub ahead of print]).

Early education and continuous support provide reinforcement of the need for adherence to therapy, as well as an opportunity to personalize the treatment and adjust settings and equipment as needed for each individual patient. Although specific guidelines for the best timing of the educational intervention are still lacking, evidence suggests that long-term compliance with CPAP might be determined as early as 2 weeks after therapy is initiated (Aloia et al. *J Clin Sleep Med*. 2005;1[4]:346). Therefore, educational programs should be readily available for prospective and new CPAP users in order to enhance their understanding of OSA and knowledge about CPAP treatment and to provide them with a venue for reviewing and managing compliance-related issues. Such programs can be run by dedicated sleep technologists, respiratory therapists, or nurses in clinics where physician availability is more limited.

### Summary

CPAP remains the most effective treatment for OSA, though adherence is a struggle for many patients. Identifying the best mask for a given patient, determining whether humidification or an expiratory pressure drop should be added and making early and frequent contact after prescription can all assist in improving long-term CPAP use. Regular review of adherence data with the patient is also important, modifying the therapy as necessary to optimize comfort, understanding that such changes may necessitate a subsequent pressure adjustment to maintain disease control. Implementing a comprehensive approach to managing patients using CPAP therapy can impact compliance by reducing treatment-related complaints and improving comfort.

Dr. Ebben is Assistant Professor of Psychology in Clinical Neurology, Department of Neurology; and Dr. Krieger is Associate Clinical Professor, Departments of Medicine, Neurology, and Genetic Medicine; Weill Cornell Medical College of Cornell University, New York, New York.

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# CPAP's antihypertensive benefit holds up in real world

BY SUSAN LONDON

Frontline Medical News

MINNEAPOLIS – Continuous positive airway pressure works similarly well at lowering blood pressure in real-world clinical practice as in clinical trials, according to a cohort study of 880 patients with sleep-disordered breathing and hypertension.

The patients, 598 with hypertension that responded to therapy and 282 with idiopathic resistant hyper-



**Results were similar in the resistant hypertension and non-resistant hypertension groups.**

DR. WALIA

tension, were all treated at a tertiary-care sleep disorders center between 2010 and 2013.

On average, a year after starting continuous positive airway pressure (CPAP), they had a reduction of 3.0

## VITALS

**Key clinical point:** The association between CPAP and reductions in blood pressure in clinical practice appears to be stronger.

**Major finding:** One year after starting CPAP, patients had a reduction in blood pressure of 2 to 3 mm Hg, re-

mm Hg in systolic blood pressure, 2.2 mm Hg in diastolic blood pressure, and 2.5 mm Hg in mean arterial pressure in analyses adjusted for potential confounders, researchers reported at the annual meeting of the Associated Professional Sleep Societies.

The benefit was similar regardless of whether hypertension was resistant or not, although patients with the resistant form had higher blood pressure – especially systolic blood pressure – at this time point.

“Our real-world experience is consistent with the blood pressure reduction seen with the use of CPAP in the rigorous clinical trials,” commented lead researcher Dr. Harneet K. Walia, assistant professor of family

medicine with the sleep disorders center at the Cleveland Clinic. “The clinic-based effectiveness data of CPAP on blood pressure in this pragmatic clinical study were similar in the resistant hypertension and non-resistant hypertension groups.”

**Data source:** A clinic-based cohort study of 880 patients with sleep-disordered breathing and hypertension.

**Disclosures:** Dr. Walia disclosed no relevant conflicts of interest.

regardless of whether their hypertension was resistant or not.

Study findings were essentially the same when neck size was substituted for body mass index as a potential confounder (although the multivariate model had a better fit) and when analyses were restricted to the 82% of patients who were adherent to CPAP, according to self-report.

In an interview, session cochair Dr. Cathy Anne Goldstein, assistant professor of neurology at the University of Michigan, Ann Arbor, said, “This

is a promising study that does show the association of treating obstructive sleep apnea with CPAP and reducing blood pressure. This was nice because it showed it wasn't just the patients who were refractory – it was all comers with hypertension who had a benefit.”

“This isn't new, but it's confirmatory of what some other studies have shown,” she added. “The more information we can get, the better, because there have been some conflicting results.”

## VIEW ON THE NEWS

**Dr. Paul A. Selecky, FCCP, comments:**

This is a nice and natural extension from clinical trials to everyday practice in the treatment of hypertension in sleep apnea patients.



# Cancer risk seen in insomnia with very short sleep duration

BY SUSAN LONDON

Frontline Medical News

MINNEAPOLIS – People who have the type of insomnia characterized by a sharply shortened duration of sleep are at increased risk for cancer, a longitudinal cohort study showed.

In the study of more than 1,600 adults from the general population, those who reported insomnia and slept 5 hours or less per night as determined by polysomnography had more than double the adjusted cancer risk of their insomnia-free counterparts who slept longer. But the association was no longer significant after depression was controlled for.

“Insomnia with severe short sleep duration is associated with increased risk of cancer, particularly in those with comorbid depression,” commented first author Julio Fernandez-Mendoza, Ph.D., of the sleep research and treatment center, department of psychiatry, Penn State College of Medicine, Hershey.

Previous research has established a dose-response relationship between objectively measured sleep duration and other adverse health outcomes, he noted. “For us, basically, objective sleep duration is a biomarker, is an

assay, is the best we have right now. ... These findings expand on our previous studies, and it appears that we can continue using this assay to explore the medical morbidity associated with this insomnia phenotype.”

In an interview, session cochair Dr. Ruth M. Benca, director of the center for sleep medicine and sleep research



**Insomnia patients who slept more than 5 hours had no elevated odds of cancer.**

DR. FERNANDEZ-MENDOZA

at the University of Wisconsin–Madison, commented, “The whole connection between sleep and cancer has now come to the fore with some of the recent studies showing, for example, that sleep apnea seems to be a risk factor for the ultimate development of cancer. And these new data suggest that insomnia, or insomnia and depression, may also play a role. We need more mechanistic studies to understand how those links may work.”

The picture is complicated by over-

laps between apnea and insomnia, she noted. “People with apnea can have high rates of insomnia, and both insomnia and apnea can be associated with fragmented sleep or insufficient sleep. So is it the insufficient sleep that's a problem? Do hypoxemia and apnea also contribute? There are some animal studies that suggest that hypoxemia is related to cancer progression.”

In the study, the investigators analyzed data from 1,620 individuals in the Penn State cohort who had no history of cancer at baseline. Insomnia was defined as self-reported insomnia present for at least 1 year, and very short sleep duration was defined as 5 hours or less as determined by polysomnography.

After a follow-up of about 15 years, 12.3% of the individuals experienced incident cancer, defined as a cancer diagnosis or death from the disease.

In an analysis adjusted for traditional confounders (sex, age, race, apnea-hypopnea index, body mass index, diabetes, and hypertension), relative to non-insomnia patients who slept more than 5 hours nightly, insomnia patients who slept 5 hours or less had significant 2.73-fold higher odds of incident cancer.

However, the association was no longer significant after additional adjustment for depression. “This makes sense because we do know very well two things: the strong association of depression with cancer, and second, the strong association of insomnia with depression. They have a lot in common, particularly inflammation. They have in common fatigue also,” Dr. Fernandez-Mendoza said at the annual meeting of the Associated Professional Sleep Societies.

Similarly, the association was not significant after additional adjustment for smoking and alcohol use. “Because these are basically behavioral factors, many insomniacs stop smoking or stop using so much alcohol, just related to the sleep hygiene thing,” he commented.

The investigators have not yet assessed whether insomnia with very short sleep duration is associated with specific types of cancer, according to Dr. Fernandez-Mendoza.

Of note, insomnia patients who slept more than 5 hours had no elevated odds of cancer. Nor did non-insomnia patients who slept 5 hours or less.

Dr. Fernandez-Mendoza disclosed no relevant conflicts of interest.



# Poor sleep linked to cortical amyloid burden

BY SUSAN LONDON

Frontline Medical News

MINNEAPOLIS – People who report feeling more sleepy and less rested have elevated levels of amyloid in regions of the brain commonly involved in Alzheimer's disease, according to a cohort study presented at the annual meeting of the Associated Professional Sleep Societies.



**'It's kind of tantalizing that sleep may be a tool that we can use to prevent or delay Alzheimer's pathology.'**

MS. SPRECHER

Researchers studied 98 asymptomatic, cognitively healthy late- to middle-age adults from the WRAP (Wisconsin Registry for Alzheimer's Prevention) program, the majority of whom were at elevated risk for the disease because of family history.

Self-reported somnolence, poorer sleep quality, and sleep problems were significantly correlated with higher levels of amyloid deposition in the cortex overall and in four subregions typically affected in Alzheimer's disease.

"It does appear that there is an association between amyloid burden and sleepiness, and that relationship is present in adults who are cognitively healthy but who are at risk of developing Alzheimer's disease in the fu-

ture. They are fairly young in terms of amyloid pathology," said first author Kate Sprecher, a PhD candidate in the neuroscience training program at the University of Wisconsin-Madison. She acknowledged that the findings may differ in a cohort not enriched for people at elevated risk.

"We can't say from these data whether sleep is driving amyloid deposition or whether amyloid deposition is disrupting sleep," she said. "Nonetheless, it's kind of tantalizing that sleep may be a tool that we can use to prevent or delay Alzheimer's pathology. We may be able to intervene early in the disease, when people are actually able to respond to treatment, because typically, current drugs are targeting later disease, when a great deal of neurodegeneration has already taken place. So sleep may be something that we can target really early."

The researchers plan to investigate the observed association using objective measures of sleep and obstructive sleep apnea (OSA), according to Ms. Sprecher. "And we'll do some longitudinal follow-up as well in our cohort to see how sleep changes might relate to actual progression of the disease."

Study participants completed the Medical Outcomes Study (MOS) Sleep Scale and the Epworth Sleepiness Scale (ESS). Amyloid deposition in the brain was measured by positron-emission tomography performed with Pittsburgh Compound B.

The participants were 63 years old, on average, and two-thirds were fe-

male. Overall, 76% had a family history of Alzheimer's, and 34% were positive for the APOE4 allele, which is associated with risk of this disease.

Analyses adjusted for these and other confounders showed a correlation ( $P$  less than or equal to .05) between somnolence on the MOS Sleep Scale – the average of scores for drowsiness, trouble staying awake, and napping – and the burden of amyloid in the left supramarginal gyrus (correlation [ $r$ ] = 0.22), the left frontal medial orbital cortex ( $r$  = 0.21), and the left frontal inferior orbital cortex ( $r$  = 0.21).

Poorer quality of sleep was significantly correlated with amyloid burden in the cortex overall ( $r$  = 0.25) as well as in the left and right precuneus ( $r$  = 0.23 and 0.25), the right supramarginal gyrus ( $r$  = 0.23), the left and right frontal medial orbital cortex ( $r$  = 0.29 and 0.29), and the left and right frontal

inferior orbital cortex ( $r$  = 0.26 and 0.25). Scores on the Sleep Problem Index were also linked to greater burden in some of these cortical areas.

Although ESS scores were significantly correlated with MOS scores, they were not directly correlated with amyloid burden in any of the regions studied. "This could be because the two questionnaires probe slightly different aspects of sleepiness," Ms. Sprecher said in an interview. "The ESS asks how likely you are to fall asleep in several common situations such as while watching TV or driving a car. The MOS asks whether you take naps, feel sleepy during the day, or feel that you get enough sleep at night. Therefore, the MOS may be better at probing how adequate your sleep is, even if you are managing to stay awake during the day."

Ms. Sprecher had no disclosures.

## VIEW ON THE NEWS

### Dr. Vera DePalo, FCCP, comments:

As we learn more about the benefits of healthy sleep, we begin to recognize how integral sleep is to maintaining a healthy, well-functioning body.

The work described in this article is intriguing.

It provides a potential first point of recognition for a link between the poor sleep and the pathologic findings seen in those

individuals who are at risk for Alzheimer's disease.

While it was the subjective sleep scale used to assess sleepiness in the work described which correlated with amyloid deposition, it will be very interesting to see if the objective measures of impaired sleep correlate

as well.

More study is needed to better understand the potential link.



## OSA screen pitched for Medicare

Initial visit from page 1

have OSA. That number is expected to grow with the rising obesity rates, he said. Untreated OSA can increase the risk of hypertension, heart disease, type 2 diabetes, and stroke, said Dr. Morgenthaler, who is professor of medicine at the Mayo Clinic in Rochester, Minn.

The AASM has been lobbying Congress to include a validated OSA screen in the initial Medicare visit and found sponsors in Rep. Michael Burgess (R-Tex.) and Rep. Bobby Rush (D-Ill.). In May, the two congressmen introduced a bill (H.R. 4695) that would do just that.

"This important legislation addresses the barriers that prevent new Medicare beneficiaries from receiving what we know to be required sleep apnea services," Dr. Morgenthaler

said at the annual meeting of the Associated Professional Sleep Societies.

Rep. Erik Paulsen (R-Minn.), who recently signed on to the bill as a



**AASM wants to make it easier for sleep medicine specialists to care for Medicare patients from start to finish.**

DR. MORGENTHALER

cosponsor, told AASM attendees that adding an OSA screen to the initial Medicare visit would help increase detection of disease, raise patient awareness, and "improve health care quality and reduce costs to the Medicare pro-

gram," over the long term.

The AASM is asking its members to back the legislation and educate local lawmakers and patients through the group's Seniors Sleep Campaign.

The association also wants to make it easier for board-certified sleep medicine specialists to care for Medicare patients from start to finish, including durable medical equipment such as continuous positive airway pressure devices.

Currently, antikickback laws prevent sleep specialists and sleep centers from directly providing therapeutic durable medical equipment to Medicare patients, said Dr. Morgenthaler.

The AASM has developed model language for an exception to that statute, which it hopes legislators or regulators will approve, he said.

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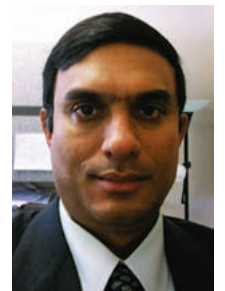
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## VIEW ON THE NEWS

### Dr. Krishna Sundar, FCCP, comments:

This is a bold definitive step from AASM to highlight benefit of early recognition of obstructive sleep apnea.

Given the high prevalence of OSA and how it interfaces with a variety of chronic problems, this push to screen Medicare recipients underscores the need for understanding of the impact that treating sleep-disordered breathing affords in this population by reducing health care costs and morbidity from chronic disease.



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