EXAMPLES T Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



The guidelines, written by Dr. Shawn Ralston (shown here) and colleagues, recommend preventive palivizumab for preemies.

Support, observation best for bronchiolitis

BY TARA HAELLE Frontline Medical News

he main treatment for bronchiolitis in young children should be support and observation, according to new clinical practice guidelines for diagnosing, managing, and preventing bronchiolitis.

The guidelines apply to children aged 1-23 months and emphasize clinical diagnosis and no medications except nebulized hypertonic saline for infants hospitalized with bronchiolitis, wrote Dr. Shawn L. Ralston, Dr. Allan S. Lieberthal, and their associates (Pediatrics 2014 October 27 [doi:10.1542/peds.2014-2742]). These guidelines

update and replace the ones issued by the American Academy of Pediatrics in 2006 (Pediatrics 2006 118:1774-93). The findings are based on a review of the evidence in the Cochrane Library, Medline, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) from 2004 through May 2014.

The most notable change to these updated guidelines, according to Dr. Lieberthal, is the preventive recommendation for palivizumab, which is now not indicated for children born at 29 weeks' gestation or older unless they have hemodynamically significant heart disease

See Guidelines • page 12

Vitamin D failed to improve ICU patients' outcomes

No differences in 6-month mortality.

BY AMY KARON Frontline Medical News

igh-dose vitamin D did not improve outcomes in critically ill, vitamin D-deficient patients, compared with placebo, researchers reported in JAMA and at the annual congress of the European Society of Intensive Care Medicine.

Although the study was adequately powered, length of stay did not differ between the vitamin D and placebo groups, said Dr. Karin Amrein of the Medical University of Graz (Austria), and her associates. "In the overall cohort, hospital and 6-month mor-

tality rates were numerically lower in the vitamin D_3 group, but these differences were not significant," the researchers said.

A subgroup of patients with severe vitamin D deficiency did have significantly lower hospital mortality when treated with vitamin D, compared with placebo, but the effect "should be considered hypothesis generating and requires further study," the investigators concluded.

The randomized, double-blind, single-center trial enrolled 492 critically ill medical and surgical pa-

See Vitamin D • page 13

S Ν D

News New IPF options Nintedanib, pirfenidone *approved* for pulmonary fibrosis. • 6

CPR plus ECMO

Survival rate is nearly double vs. CPR only. • 8

Critical Care Medicine Statin flops for ARDS

Simvastatin shows no benefit in large trial. • 14

Pulmonary Medicine Pneumonia readmissions

QI effort boosts diagnoses, cuts rates by 7%. • 22

News From CHEST Trial participation

The CHEST Clinical Trials Registry offers a wealth of research information. • 32

SLEEP STRATEGIES The how, why, and where of sleep telemedicine

BY DR. BARRY FIELDS

e practice in a medical world that physicians of a prior generation could never have envisioned. Not only do we have diagnostic modalities that can yield more rapid and definitive

answers for a puzzling patient, but we can also treat and monitor patients who are dozens, if not hundreds, of miles away from our clinic. Sleep medicine is an area ripe for implementation of telemedicine, but building a successful sleep

telemedicine program is a tricky endeavor, requiring resources, a clinical demand, and opportunities for such implementation. Despite these challenges, I have found practicing sleep in this

See Sleep Strategies • page 34



CHANGE SERVICE REQUESTED

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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:

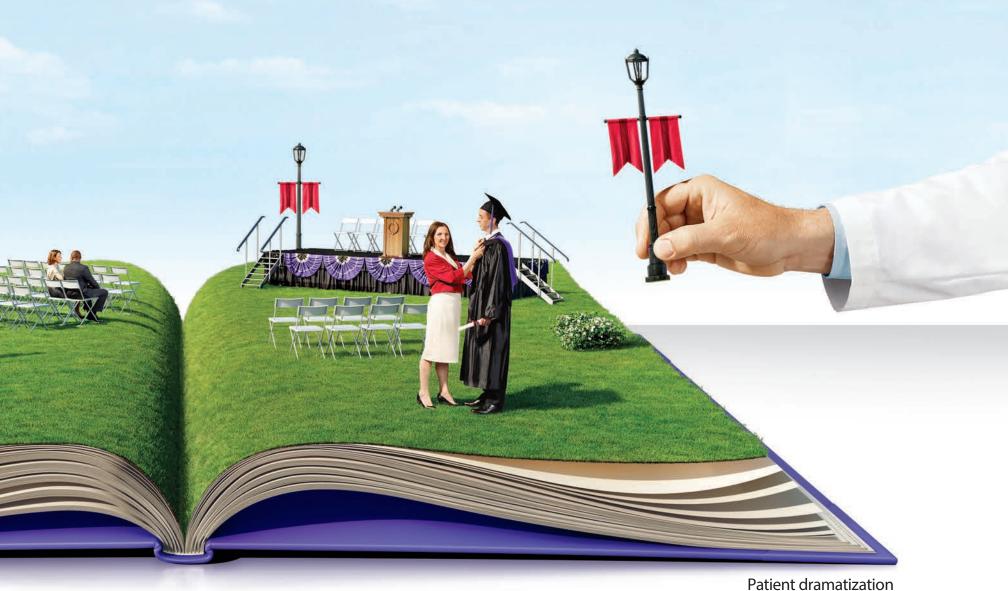
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NIVERSITY My Son's Graduation

- 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 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × 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 × 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 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.*





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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.

Rx only

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 <u>www.OPSUMITREMS.com</u> 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 \geq 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 CVP3A4. 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)

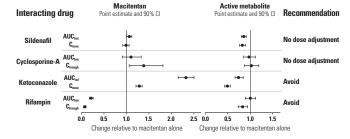
Drug Interactions

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

<u>Effect of other drugs on macitentan</u>: 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

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Nintedanib, pirfenidone OK'd for pulmonary fibrosis

BY M. ALEXANDER OTTO Frontline Medical News

he Food and Drug Administration approved two new oral medications for idiopathic pulmonary fibrosis, Boehringer Ingelheim's nintedanib (Ofev) and Roche's pirfenidone (Esbriet).

The drugs significantly slowed the decline of forced vital capacity (FVC), compared with placebo, NEWS in phase III testing. They did not significantly reduce mortality. The FDA granted both agents fast track, priority review, orphan product, and breakthrough designations. Both were also approved ahead of schedule, according to the agency.

Each of the drugs should be available for patients within the next 2 weeks, according to their manufacturers.

For pirfenidone, already on the market in Europe and Canada, Roche said it plans "a comprehensive patient support program designed to help with access, financial support, and ongoing education."

For nintedanib, Boehringer Ingelheim plans "a comprehensive patient support program that will provide a broad range of financial and nursing

support services," called "Open FDΔ Doors'

In testing, the most frequent serious adverse reactions with

nintedanib, versus placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). Pneumonia (0.7% vs. 0.6%), lung cancer (0.3% vs. 0%), and MI (0.3% vs. 0.2%) were the most common fatal adverse events.

The most common side effects of

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Test your ICD-10 skills How well can you code a case of acute bronchiolitis? • 31

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

VIEW ON THE NEWS

Dr. Eric Gartman, FCCP, comments: The approval of these two agents for IPF was long awaited and is an encouraging step toward treating this progressive, fatal disease. While the therapeutic results from these medicines are far from a cure or even a complete arrest of progression, they represent the first beneficial options

nintedanib were diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight loss, and high blood pressure. Nintedanib is not recommended for patients who have moderate to severe liver problems or are pregnancy class D. Women of childbearing potential should use contraception for at least 3 months after stopping the drug, according to the FDA.

For pirfenidone, the most serious adverse events vs. placebo were liver enzyme elevations (3.7% vs. 0.8%), sensitivity to light or rash (9.0% vs. 1.0%), and gastrointestinal side effects that caused 2.2 % of patients to discontinue treatment, compared with 1.0% of those who received placebo.

The most common side effects of pirfenidone were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, loss



in a disease marred by disappointing treatment attempts in the past. We can be hopeful that this marks the beginning of advancing research and the additional availability of treatments in the future, and that the reported cost of nearly \$100,000 a year for one of

these agents doesn't complicate and limit treatment of IPF further.

of appetite, gastroesophageal reflux, sinusitis, insomnia, decreased weight, and arthralgia.

The FDA warned about use of pirfenidone in patients with severe liver problems or end-stage kidney disease, or in those who require dialysis. Patients taking pirfenidone also must monitor and guard against sun exposure.

Clinical trials of pirfenidone included 1,247 idiopathic pulmonary fibrosis patients. In one with 555 patients, 17% of pirfenidone patients had decline in forced vital capacity of at least 10% after a year, compared with 32% who received placebo, Roche said.

Trials of nintedanib included 1,231 patients. One trial with 513 patients showed a relative reduction in annual forced vital capacity of 52% (-115 vs. -240 mL for placebo) at 1 year, Boehringer Ingelheim noted.

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NEWS 7

Vaccine cut resistant IPD in kids

BY SHARON WORCESTER Frontline Medical News

PHILADELPHIA – The 13-valent pneumococcal conjugate vaccine introduced in 2010 has led to a substantial reduction in cases of antibiotic-resistant invasive pneumococcal disease, IPD, in children under the age of 5 years, resulting in early achievement of a Healthy People 2020 goal, according to Dr. Sara Tomczyk.

Between 2010 and 2013, 378 cases of antibiotic-resistant invasive pneumococcal disease – or 3.5 per 100,000 children – were identified from 10 Active Bacterial Core (ABC) sites, marking a 62% decrease from the 745 cases (9.3 per 100,000 children) identified between 2005 and 2009, Dr. Tomczyk of the Centers for Disease Control and Prevention reported.

Similarly, cases of antibiotic resistant and multidrug-resistant invasive pneumococcal disease and cases from PCV5-type invasive pneumococcal disease covered by the 13-valent vaccine but not by the previously available 7-valent vaccine decreased by 93% and 86%, respectively. Nonvaccine-type antibiotic-resistant cases increased in incidence from 2.5 to 3.1 per 100,000.

The cases reviewed were from the CDC's ABC surveillance sites, which include about 29 million patients, or 10% of the U.S. population. Isolates were serotyped, and antimicrobial susceptibility testing was performed at a reference laboratory. Bacterial isolates were considered antibiotic resistant if they exhibited intermediate or resistant patterns to at least 1 antimicrobial class, and were considered multidrug resistant if they were resistant to at least 3 antimicrobial classes.

The findings demonstrate that the Healthy People 2020 goal to reduce cases of antibiotic-resistant IPD among children under 5 from 9.3 to 6.0 cases per 100,000 was achieved in 2011 – 9 years early, and they underscore the importance of appropriate antimicrobial use and a sustained high rate of PCV13 vaccination, Dr. Tomczyk said at the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

About 85% of U.S. children have received the recommended four doses.

Dr. Tomczyk had no disclosures.

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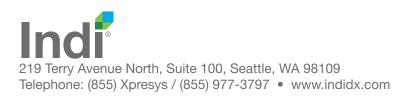
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How ICUs, health providers can prepare for Ebola

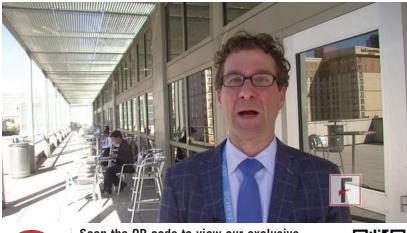
ARTICLES BY WHITNEY McKNIGHT Frontline Medical News

AUSTIN, TEX. – Why would travel restrictions make the Ebola epidemic worse in West Africa and expand its spread to U.S. shores? What can American intensive care units do to prepare, even if they aren't designated Ebola centers? And are there lessons medical professionals and policymakers can apply from the successes and failures of the AIDS epidemic 30 years ago?

In a video interview at CHEST 2014, the annual meeting of the American College of Chest Physicians, Dr. Lewis Rubinson offered answers to those questions and perspectives on the current American response to the Ebola outbreak. Dr. Rubinson recently returned from treating more than 300 Ebola patients in Sierra Leone as a consulting physician for the World Health Organization.

"Honestly, I think if we don't get it under control in the next few months in West Africa, there will be sporadic cases coming back [to the United States] for as long as we can think of," cautioned Dr. Rubinson, director of the R. Adams Cowley Shock Trauma Center at the University of Maryland, Baltimore.

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Scan the QR code to view our exclusive interview with Dr. Lewis Rubinson, of the R. Adams Cowley Shock Trauma Center at the University of Maryland, Baltimore.

ECMO plus CPR boosts survival seen with CPR only

AUSTIN, TEX. – Extracorporeal membrane oxygenation delivered during cardiopulmonary resuscitation allowed nearly twice as many patients to survive after discharge when compared against typical CPR-only procedures in a small, retrospective study.

"It's no secret that conventional CPR is not terrifically successful," Graham Peigh, a second-year medical student at Jefferson Medical College in Philadelphia, said during the Hot Topics in Pulmonary and Critical Care session at the annual meeting of the American College of Chest Physicians. "Extracorporeal membrane oxygenation [ECMO] gives patients a second chance at life." viously reported meta-analysis (J. Gen. Intern. Med. 1998;13:805-16) to 29% (P = .04).

When an arrested patient does not respond to CPR, cannulation through the femoral artery and vein can be combined with compressions to improve chances of survival.

In their analysis, Mr. Peigh and his colleagues found that the survival rate with full neurologic recovery was 29% in the 24 cases in which ECMO was added to conventional CPR after the patients failed to respond to CPR alone.

ECMO support was delivered in a number of scenarios, ranging from acute myocardial infarction to malig-

Mr. Graham Peigh (right) is shown with Dr. Hitoshi Hirose of Thomas Jefferson University Hospital, Philadelphia.

Mr. Peigh and his colleagues retrospectively analyzed 100 ECMO procedures performed on adults at a single teaching hospital during 2010-2013 and found that when ECMO was added to CPR, the survival rate to discharge went from 15% as calculated in a prenant arrhythmia to at least one case each of drug overdose induced cardiac arrest, septic shock, postcardiotomy failure, and acute rejection.

The ECMO support was provided for a mean of 5 days. The mean age for all patients studied was 47 years, and 15 were male. All cases followed a 24-hour hypothermia protocol. Six of the EC-MO-CPR patients

died post ECMO of anoxic brain injury, stroke, or sepsis while still in the hospital, but the remaining seven patients (54%) survived after discharge and made full neurologic recoveries. The other 11 died during ECMO-CPR. *Continued on page 10*

Insights on genetic testing for anticoagulant therapy





To view our exclusive interview with Dr. Steven Hollenberg at CHEST 2014, scan the QR code or visit our video library at chestphysician.org.

AUSTIN, TEX. – Genetic testing holds promise for guiding the prescribing of antiplatelet therapies, particularly clopidogrel, but "we're not there yet" for the use of this testing in clinical practice, according to Dr. Steven Hollenberg, who is the director of the coronary care unit at Cooper University Hospital in Camden, N.J.

Genetic testing for clopidogrel responsiveness "certainly makes good sense, but I think we're going to have to wait for good data" that better inform clinical decision making.

Dr. Hollenberg discussed the implications of the negative results of the ARCTIC trial, which showed platelet function testing with antiplatelet therapy adjustment failed to improve clinical outcomes compared with standard unmonitored thienopyridine therapy in elective percutaneous coronary intervention.

Dr. Hollenberg also analyzed the results of other studies that are relevant to optimal antiplatelet and anticoagulant therapy, including the surprising outcomes of the WOEST trial.



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A new treatment option is here for your patients living with Idiopathic Pulmonary Fibrosis

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Indication

Esbriet® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

Select Important Safety Information

Elevated liver enzymes: Increases in ALT and AST >3× ULN have been reported in patients treated with Esbriet. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with Esbriet 2403 mg/day in the three phase 3 trials had a higher incidence of elevations in ALT or AST (\geq 3× ULN) than placebo patients (3.7% vs 0.8%, respectively). Elevations \geq 10× ULN in ALT or AST occurred in 0.3% vs 0.2% of patients in the Esbriet 2403 mg/day group and placebo group, respectively. Increases in ALT and AST \geq 3× ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to Esbriet have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiating Esbriet, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary.

Photosensitivity reaction or rash: Patients treated with Esbriet 2403 mg/day in the three phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Most photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Instruct patients to avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: In clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported by patients in the Esbriet treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% vs 5.8% of patients in the 2403 mg/day group compared with the placebo group, respectively; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event vs 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea (36% vs 16%), rash (30% vs 10%), abdominal pain (24% vs 15%), upper respiratory tract infection (27% vs 25%), diarrhea (26% vs 20%), fatigue (26% vs 19%), headache (22% vs 19%), dyspepsia (19% vs 7%), dizziness (18% vs 11%), vomiting (13% vs 6%), anorexia (13% vs 5%), gastroesophageal reflux disease (11% vs 7%), insomnia (10% vs 7%), weight decreased (10% vs 5%), and arthralgia (10% vs 7%) in the Esbriet and placebo treatment groups, respectively.

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

The concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors (eg, enoxacin) is not recommended because it significantly increases exposure to Esbriet. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of Esbriet and avoided during Esbriet treatment. If fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

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

The concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of Esbriet, and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to Esbriet treatment and avoid concomitant use of Esbriet and a strong CYP1A2 inducer.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to InterMune at 1-888-486-6411.

Please see Brief Summary of Prescribing Information on adjacent pages for additional important safety information.



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Continued from page 8

During ECMO-CPR, 11 patients died of anoxic brain injury, stroke, metabolic acidosis, bowel necrosis, and family withdrawal of life support. Predictors of ECMO death were a pre-ECMO creatinine level of 1.7 mg/dL (P = .02) and the

presence of acidosis (P = .04).

The ECMO survivor cohort also had "encouraging" organ function results, with kidney and liver function remaining essentially unchanged after discharge. "Two of the patients who died of anoxic brain injuries were able to donate multiple organs for transplant," Mr. Peigh said. Previously reported ECMO data have shown there is at least a 20% increase in survival without notable neurologic effect, compared with conventional CPR (Lancet 2008;372:554-61; Crit. Care Med. 2011;39:1-7).

However, since these data were derived from centers where code teams were available at all times to treat a high volume of cardiac arrest patients, Mr. Peigh said the results – although indicative of the procedure's value – "were not generalizable" to all institutions.

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Rx only

BRIEF SUMMARY

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Disorders

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

ADVERSE REACTIONS

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

- Liver Enzyme Elevations [see Warnings and Precautions]
- Photosensitivity Reaction or Rash [see Warnings and Precautions]
- Gastrointestinal Disorders *[see Warnings and Precautions]*

ESBRIET[®] (pirfenidone)

Clinical Trials Experience

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

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

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

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

The most common adverse reactions with an incidence of $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 1.

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

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

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

Postmarketing Experience

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

Blood and Lymphatic System Disorders Agranulocytosis Immune System Disorders Angioedema Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

Comorbidities in opioid users with sleep apnea

BY SHARON WORCESTER Frontline Medical News

AUSTIN, TEX. - Any association between opioid use and death in patients with sleep apnea cannot be explained by sleep apnea alone, according to a retrospective analysis of data from the prospective observational DREAM study.

In 1,867 patients with moderate or severe sleep apnea who were on an opioid medication, no association was seen between opioid use and severity of sleep-disordered breathing, even with increasing doses, Dr. Husham Sharifi reported at the annual meeting of the American College of Chest Physicians.

Further, when opioid use was analyzed as an unadjusted variable, it was associated with an increase in mortality (odds ratio, 1.53), but this effect was attenuated by adjustment for sleep apnea (OR, 1.52), and was further attenuated – to the point where it was no longer statistically significant – by adjustment for both sleep apnea and

VITALS

Key clinical point: Comorbid conditions may explain the link between opioid use, sleep apnea, and death.

Major finding: Opioid use was not significantly associated with mortality after adjustment for sleep apnea and comorbidities (odds ratio, 1.37).

Data source: A retrospective analysis of data for 1,867 patients from the prospective DREAM cohort.

Disclosures: Dr. Sharifi reported having no disclosures.

Charlson Comorbidity Index (OR, 1.37), said Dr. Sharifi, who was an attending physician at Brigham and Women's Hospital, Boston, at the time of the research. He is now a fellow at Stanford (Calif.) University.

Sleep apnea remained an independent predictor of mortality even after adjustment for opioid use and Charlson Comorbidity Index, he said.

The DREAM study, which stands for Determining Risk of Vascular Events by Apnea Monitoring, includes a well-defined cohort of patients at three Veterans Administration sleep centers who were referred for overnight polysomnography for suspected sleep-disordered breathing between 2000 and 2004.

All patients had an Apnea-Hypopnea Index score greater than 15, indicating moderate to severe sleep apnea, and all were on opioid medication. The patients were followed for between 3 and 10 years, with follow-up ending Dec. 31, 2010.

Opioid use has boomed over the past 20 years – by more than 700%, Dr. Sharifi said. While there does not appear to be a significant impact of opioid use on daytime respiration, there are some limited data suggesting that it may be associated with sleep-disordered breathing.

The findings, though limited by the observational nature of the study and possible selection bias as the DREAM cohort is a referral population, suggest sleep apnea death is likely explained by an increased prevalence of risk factors in patients who take opioids and have sleep apnea.

DRUG INTERACTIONS

CYP1A2 Inhibitors

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

ESBRIET[®] (pirfenidone)

Strong CYP1A Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET [see Clinical Pharmacology section 12.3 in full Prescribing Information]. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended Monitor for adverse reactions and consider discontinuation of ESBRIET as needed [see Dosage and Administration section 2.4 in full Prescribing Information].

Moderate CYP1A Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

CYP1A2 Inducers

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m² basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m² basis at a maternal dose of 1000 mg/kg/day).

Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed [see Dosage and Administration section 2.2 in full Prescribing Information

ESBRIET[®] (pirfenidone)

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

Renal Impairment

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

Smokers

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

OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

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

Photosensitivity Reaction or Rash

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

Gastrointestinal Events

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

Smokers

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

Take with Food

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

InterMune, Inc Brisbane, CA 94005 USA

Reference: 1. ESBRIET full Prescribing Information. InterMune, Inc. October 2014.



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Manufactured for

NOVEMBER 2014 • CHEST PHYSICIAN

Observation is best for bronchiolitis

Guidelines from page 1

or chronic lung disease of prematurity (those born at less than 32 weeks' gestation who needed at least 21% oxygen for their first month). Premature infants who qualify for prophylactic palivizumab should get five monthly doses during respiratory synctial virus season.

VITALS

Key clinical point: Bronchiolitis should be diagnosed clinically and treated with support.

Major finding: Most treatments should not be administered because outcomes are not improved.

Data source: The findings are based on a review of the evidence in the Cochrane Library, Medline, and CINAHL from 2004 through May 2014.

Disclosures: Funding was provided by the American Academy of Pediatrics with travel support from CHEST, the American Academy of Family Physicians, the American Thoracic Society, and the American College of Emergency Physicians for their representatives.

Dr. Lieberthal noted in an interview that several other recommendations state that certain treatments should not be used at all rather than simply not being routinely used. These include albuterol, epinephrine, corticosteroids, chest physiotherapy, and antibiotics.

"Bronchiolitis is a self-limited viral illness," he said. Because it is diagnosed by signs and symptoms, no lab tests, oximetry, imaging, or other tests are needed, and treatment

involves only support and observation. "None of the treatments that have been tested have been shown to affect the outcome of the illness," said Dr. Lieberthal, who practices general pediatrics and clinical pediatric pulmonology at Kaiser-Permanente in Panorama City, Calif.

Dr. Ralston noted in an interview that a new recommendation exists for using hypertonic saline to children who are hospitalized for bronchiolitis (although not in the emergency department), but the evidence for it is weak and its therapeutic value limited.

"This medication appears to have a slow onset and to provide a favorable response only in settings where patients are hospitalized for longer than is typical in most U.S. hospitals, as most of the studies were performed outside the U.S.," said Dr. Ralston, a pediatrician at Dartmouth-Hitchcock Medical Center, Lebanon, N.H.

The guidelines also note that clinicians "may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90%" in children, although the evidence for this recommendation is also weak. Children should receive nasogastric or intravenous fluids if they cannot maintain oral hydration.

Parents should be advised that children who avoid secondhand tobacco smoke and are exclusively breastfed for at least 6 months have a reduced risk of bronchiolitis.

Further, anyone caring for a child with bronchiolitis should disinfect their hands using an alcohol-based

rub or soap and water after direct contact with the child and the child's immediate environment.

Dr. Ralston said that important points stressed in both this recommendation and in the previous one include clinical diagnosis and avoiding exposure to tobacco smoke to reduce children's risk of bronchiolitis.

"This guideline is mostly about what you shouldn't do for the disease since, because of the high volume of the disease, bronchiolitis represents a major area of unnecessary medical intervention in children," Dr. Ralston said.

No medications except nebulized hypertonic saline are

advised for infants hospitalized with bronchiolitis.

"We know that the vast majority of children will suffer only side effects from the medications or testing typically used in bronchiolitis care.'

VIEW ON THE NEWS

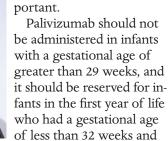
Dr. Neil Skolnik comments: These guidelines, written with clarity, give incredibly direct and

helpful direction on the diagnosis and treatment of bronchiolitis. It is great that these guidelines are coming out now, prior to RSV season.

Bronchiolitis is a clinical diagnosis and these guidelines reaffirm that there is not usually any need for x-ray or laboratory confirmation of the diagnosis.

The guidelines are primarily important for clarifying, based on the evidence, that many commonly used treatments, including albuterol, epinephrine, and steroids are not recommended for treatment of bronchiolitis as they are simply not helpful.

The guidance on administration of palivizumab is also im-



who had hemodynamically significant heart disease or chronic lung disease of prematurity.

Dr. Skolnik is professor of family and community medicine at Temple University in Philadelphia.

'Real-time' test will speed enterovirus D68 confirmation

BY LUCAS FRANKI Frontline Medical News

new lab test for enterovirus D68 is expected to speed up testing and confirmation of cases, according to a press release from the Centers for Disease Control and Prevention.

The new test is a "real-time" reverse transcription polymerase chain reaction and can identify all strains of EV-D68. The previous test could be used to detect almost any enterovirus, but was labor intensive to perform and not conducive to large-scale testing.

Of the 1,200 samples from 45 states sent to the CDC for EV-D68 testing between Aug. 1 to Oct.

10, less than 200 have been tested and about half have tested positive. The CDC now expects to be able to test around 180 samples a day and complete in 7-10 days the testing on samples received since mid-September. The new method will "reduce what would normally take several weeks to

The new method will 'reduce what would normally take several weeks to get results to a few days.'

get results to a few days," Dr. Anne Schuchat, assistant surgeon general and director of the CDC's National Center for Immunization and Respiratory Diseases, said in the press release.

As with other enteroviruses, the CDC expects new cases of EV-D68 will decrease in the fall, but faster testing will

more accurately show trends of the disease and will help to monitor changes in the outbreak as it

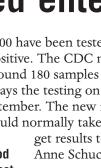
VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: Enteroviral illness has always been one of the reasons for asthma exacerbations in August and September. Enterovirus D68 certainly was rampant and especially virulent this summer and fall in the United States. If



an exact diagnosis is necessary for certain patients, this new lab test will be welcomed.

winds down, according to the CDC press release.



DR. SCHUCHAT

CRITICAL CARE MEDICINE 13

Similar mortality at 6 months

JOSS/FOTOLIA.CON

Vitamin D from page 1

tients with serum vitamin D levels of 20 ng/mL or less. Patients received placebo or vitamin D₃ at a loading dose of 540,000 IU, followed by a monthly maintenance dose of 90,000

compared with 35% of the placebo group (hazard ratio, 0.81). Six-month mortality was 35% for the vitamin D_3 group, compared with 43% for the placebo group (HR, 0.78).

Among 200 patients with severe vitamin D deficiencies of 12 ng/mL or less, vitamin D₃ treatment was linked to a significant 44% drop in risk of dying in the hospital, the researchers said (28.6% vs. 46.1% for placebo; HR, 0.56). But length of hospital stay and 6-month mortality rates were similar between the two groups.

Drug maker Fresenius Kabi provided study medication and a grant to support the research. The European Society for Clinical Nutrition and Metabolism and the Austrian National Bank also funded the study. Dr Amrein and one of his colleagues reported receiving lecture fees from Fresenius Kabi.



IU for 5 months, the researchers said (JAMA 2014 Sept. 29 [doi:10.1001/ jama.2014.13204]).

Length of hospital stay averaged 20 days for patients who received vitamin D and 19 days for the placebo group. Among patients who received vitamin D₃, 28% died in the hospital,

VIEW ON THE NEWS

Dr. Steven Q. Simpson, FCCP, comments: This study demonstrates potential failings of the statistical approach more than the failing of the therapy.

The authors powered the study to detect a 2-day reduction from a 14day length of stay. I cannot name any other single action - nor



combinations of actions - that can reduce the length of stay of critically ill patients by 2 days. I believe the authors must have done so because it would take substantially higher numbers of patients to show smaller reductions in length of stay, and this is a single-center study.

I don't read this as a failure of vitamin D, so much as the authors' failure to adequately consider variability in the outcome of interest and their overestimation of the assumed effect of the treatment. There is enough positive result in this study to consider it a pilot and call for a multicenter trial of higher power.

SYMBICORT 160/4.5 for the maintenance treatment of COPD

REV THE FEV

SYMBICORT offers something extra—sustained* control with better breathing starting within 5 minutes each time¹⁻³

- SYMBICORT is NOT a rescue medication and does NOT replace fast-acting inhalers to treat acute symptoms
- Mean percent change from baseline in FEV₁ was measured at day of randomization, months 6 and 12³

FAST CONTROL

Majority of FEV₁ improvement at 5 minutes each time⁺ in a subset of SUN Study patients taking SYMBICORT 160/4.5 (n=121)^{1,4}

SUSTAINED EFFECT

SYMBICORT 160/4.5 significantly improved 1-hour postdose FEV1 at 1 month and end of treatment compared to placebo, and improved predose FEV₁ averaged over the course of the study compared to placebo and formoterol, coprimary endpoints

REASSURING SENSE **OF CONTROL**

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

ained improvement in lung function was demonstrated in a nonth efficacy and safety study.

When treating patients with asthma, prescribe SYMBICORT only for

patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease

corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (eg, discontinue SYMBICORT) if possible without loss of

asthma control, and maintain the patient on a long-term asthma

control medication, such as an inhaled corticosteroid. Do not use

on low or medium dose

inhaled corticosteroids

severity clearly warrants initiation of treatment with both an inhaled

In a serial spirometry subset of patients taking SYMBICORT 160/4.5 (n=121) in the SUN Study, 67% of 1-hour postdose FEV, improvemer occurred at 5 minutes on day of randomization, 83% at month 6, and 84% at end of treatment.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.



Simvastatin shows no benefit for ARDS

BY AMY KARON Frontline Medical News

imvastatin did not improve clinical outcomes in adults with acute respiratory distress syndrome, compared with placebo in a multicenter, double-blind trial.

Despite positive findings in early-phase studies, large clinical trials have failed to show that statins benefit patients with ARDS, said Dr. Daniel

McAuley of Queen's University of Belfast, Northern Ireland, and his associates. The earlier studies used surrogate measures that do not clearly correlate with patient-specific outcomes, the researchers said. "Surrogate outcomes

that more closely track patient outcomes need to be identified," they added (N. Engl. J. Med. 2014 Sept. 30 [doi: 10.1056/NEJMoa1403285]).

The multicenter, double-blind trial comprised 540 adults with ARDS



- additional formoterol or other LABA for any reason Localized infections of the mouth and pharynx with Candida albicans has occurred in patients treated with SYMBICORT.
- Patients should rinse the mouth after inhalation of SYMBICORT Lower respiratory tract infections, including pneumonia,
- have been reported following the inhaled administration of corticosteroids
- Due to possible immunosuppression, potential worsening of infections could occur. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients
- It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur, particularly at higher doses. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids

- may occur with SYMBICORT
- Immediate hypersensitivity reactions may occur, as demonstrated by cases of urticaria, angioedema, rash, and bronchospasm
- Excessive beta-adrenergic stimulation has been associated with central nervous system and cardiovascular effects. SYMBICORT should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension
- Long-term use of orally inhaled corticosteroids may result in a decrease in bone mineral density (BMD). Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating SYMBICORT and periodically thereafter
- > Orally inhaled corticosteroids may result in a reduction in growth velocity when administered to pediatric patients
- Glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on following pages.

CRITICAL CARE MEDICINE 15

VIEW ON THE NEWS

Dr. Jennifer Cox, FCCP, comments: Because of positive findings in early-phase studies, we continue to look for a viable role of statins in the treatment of ARDS. In this study, unlike the preceding SAILS trial, the cause of ARDS was not limited to sepsis. Despite a broader

range of clinical diagnoses precipitating ARDS, the outcomes were similar. Currently, there are no data to support the routine use of statins in ARDS of any cause.

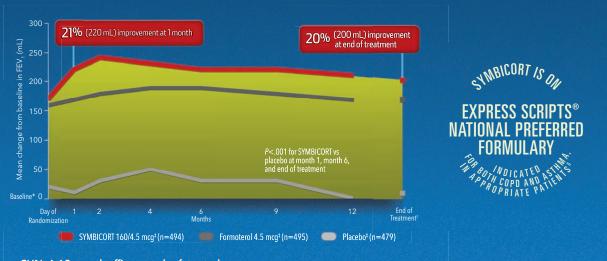


from 40 intensive care units in the United Kingdom and Ireland. Patients were randomized to enteral simvastatin or placebo, and the groups did not differ significantly in terms of number of ventilator-free days (12.6 vs. 11.5 days, respectively), days free of nonpulmonary organ failure (19.4 vs. 17.8 days), or 28-day mortality (22% vs. 26.8%). Adverse effects also were similar between the groups.

Continued on following page

SUSTAINED EFFECT OVER 12 MONTHS

Improvement in 1-hour postdose FEV₁ over the 12-month study⁴



SUN: A 12-month efficacy and safety study

SYMBICORT 160/4.5 significantly improved 1-hour postdose FEV₁ at 1 month and end of treatment compared to placebo, and improved predose FEV₁ averaged over the course of the study compared to placebo and formoterol, coprimary endpoints¹ COMPARATOR ARMS: Mean improvement in 1-hour postdose FEV₁ (mL/%) over 12 months. Month 1: SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%). Month 6: SYMBICORT 160/4.5 mcg (220 mL/21%), formoterol 4.5 mcg (190 mL/18%), placebo (30 mL/3%). End of treatment: SYMBICORT 160/4.5 mcg (200 mL/20%), formoterol 4.5 mcg (170 mL/17%), placebo (10 mL/1%). SYMBICORT 160/4.5 mcg¹ (n=494), formoterol 4.5 mcg¹ (n=495), placebo¹ (n=479).

*Baseline is defined as the predose FEV1 value on the day of randomization. *Month 12, last observation carried forward. *Administered as 2 inhalations twice daily.

SYMBICORT. Close monitoring is warranted in patients with a change in vision or history of increased intraocular pressure, glaucoma, or cataracts

- In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions
- SYMBICORT should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines
- Beta-adrenergic agonist medications may produce hypokalemia and hyperglycemia in some patients
- The most common adverse reactions ≥3% reported in asthma clinical trials included nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis
- > The most common adverse reactions ≥3% reported in COPD clinical trials included nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and upper respiratory tract infection
- SYMBICORT should be administered with caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents
- > Beta-blockers may not only block the pulmonary effect of beta-agonists, such as formoterol, but may produce severe bronchospasm in patients with asthma

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

INDICATIONS

- SYMBICORT is indicated for the treatment of asthma in patients 12 years and older (also see Boxed WARNING)
- SYMBICORT 160/4.5 is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
- > SYMBICORT is NOT indicated for the relief of acute bronchospasm

References: 1. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565. 2. SYMBICORT [package insert]. Wilmington, DE: AstraZeneca; 2012. 3. Data on File, 273071, AZPLP. 4. Data on File, 1084400, AZPLP. 5. 2014 Express Scripts Preferred Drug List.

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AstraZeneca



Ca A reassuring sense of control

CRITICAL CARE MEDICINE 16

Continued from previous page

The researchers recruited a heterogeneous cohort of patients with ARDS resulting from any cause so that findings would be generalizable.

Because recent research suggests that identification of specific phenotypes within ARDS may be possible, future studies "may identify a subpopulation of patients with ARDS who might have a greater response to simvastatin than was observed in our study," the researchers said.

The study was funded by the U.K. Efficacy and Mechanism

Evaluation Programme, a joint partnership of the Medical Research Council and the National Institute for Health Research. Dr. McAuley has financial ties to GlaxoSmithKline as well as a patent-pending application related to a novel treatment for ARDS.

SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

For Oral Inhalation Only

Rx only

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related beam from Eron. Are note to data non-controlled united in this suggest that Eron increase the track of adultate hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and ster down the stering (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [see WARNINGS AND PRECAUTIONS1

BRIEF SUMMARY

Before prescribing, please see full Prescribing Information for SYMBICORT® (budesonide/formoterol fumarate dihydrate). INDICATIONS AND USAGE

Treatment of Asthma

SVMBICORT is indicated for the treatment of asthma in patients 12 years of age and older. Long-acting beta₂-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related asimilar related dealth, whatable data from controlled unital subgest that ELAO hitchess that has no asimilar related hospitalization in pediatric and adolescent patients [see WARIMINGS AND PRECAUTIONS]. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the part of a step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the part of a long-term asthma control medication, such as inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitations of Use: • SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD) SYMBICORT 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD. <u>Important Limitations of Use:</u> SYMBICORT is not indicated for the relief of acute bronchospasm

DOSAGE AND ADMINISTRATION

SYMBICOBT should be administered twice daily every day by the orally inhaled route only. After inhalation, the patient should rinse the mouth with water without swallowing [see **PATIENT COUNSELING INFORMATION** in full Prescribing Information (17.4)]. Prime SYMBICORT before using for the first time by releasing two test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing two test sprays into the air away from the face.

More frequent administration or a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT is not recommended as some patients are more likely to experience adverse effects with higher doses of formoterol. Patients using SYMBICORT should not use additional long-acting beta₂-agonists for any reason [see doses of formoterol. Patients usin WARNINGS AND PRECAUTIONS].

Asthma

f asthma symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

Adult and Adolescent Patients 12 Years of Age and Older: For patients 12 years of age and older, the dosage is 2 inhalations twice daily (morning and evening, approximately 12 hours apart). The recommended starting dosages for SYMBICORT for patients 12 years of age and older are based upon patients'

asthma severity. The maximum recommended dosage is SYMBICORT 160/4.5 mcg twice daily.

treatment in asthma control following inhelder administration of SYMBICORT can occur within 15 minutes of beginning treatment, although maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacement with SYMBICORT 160/4.5 may provide additional asthma control.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, (e.g., replacing the lower strength of SYMBICORT with the higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids) should be considered.

Chronic Obstructive Pulmonary Disease (COPD) For patients with COPD the recommended dose is SYMBICORT 160/4.5, two inhalations twice daily. If shortness of breath occurs in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for

nediate relief.

CONTRAINDICATIONS The use of SYMBICORT is contraindicated in the following conditions:

Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required.
 Hypersensitivity to any of the ingredients in SYMBICORT.

WARNINGS AND PRECAUTIONS Asthma-Related Death

Long-acting beta₂-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and warants immation or realitient with our an immation controlsterior and LAOA, once astimat control sacheved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SVMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABA, including formoterol, one of the active ingredients in SYMBICORT. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta2-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the transmer regime, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of SYMBICORT.

SYMBICORT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta₂-agonist, not SYMBICORT, should be used to relieve acute symptoms such as shortness of breath. When prescribing SYMBICORT, the physician must also provide the patient with an inhaled, sona account of the presentance of the presentance of the provident must also provide the patient with an inhaled, short-acting beta-ragonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting beta₂-agonists on

The degramming retained with other places with other been using other minimate, short being out grammater and the second seco becargonistic, 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 SYMBICORT should not use an additional long-acting beta₂-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma or COPD.

Did betrosering of the second be interrupted. Patients should rise the mouth after inhaliation of SYMBICORT.
Pneumonic and Other Lower Respiratory Tract Infections
Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features

of pneumonia and exacerbations frequently overlap. Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids. In a 6 month study of 1,704 patients with COPD, there was a higher incidence of lung infections other than pneumonia (e.g.,

bronchitts, viral lower respiratory tract infections, etc.) in patients receiving SYMBICORT 160/4.5 (7.6%) than in those receiving SYMBICORT 80/4.5 (3.2%), formoterol 4.5 mcg (4.6%) or placebo (3.3%). Pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (1.1 %) compared with placebo (1.3%). In at 22-month study of 1.964 patients with COPD, there was also a higher incidence of lung infections other than pneumonia in patients receiving SYMBICORT 160/4.5 (8.1%) than in those receiving SYMBICORT 80/4.5 (6.9%), formoterol 4.5 mcg (7.1%) or placebo (6.2%). Similar to the 6 month study, pneumonia did not occur with greater incidence in the SYMBICORT 160/4.5 group (4.0%) compared with placebo (5.0%).

Immunosuppression Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals Chicken pox and measles, for example, can have a more series as the course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IC) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension

An open-label, nonrandomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma The particular theorem is a set of a set of the set of steroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination

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

Transferring Patients From Systemic Corticosteroid Therapy Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled cortico-steroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic cortico systemic controlsterious to less systemicany available innated controlsterious. Arter windrawa non systemic control-steriods, a number of months are required for recovery of hypothalamic-pithulary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most

susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although SYMBICORT may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary

for coping with these emergencies. During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further systemic corticosteroids during periods of stress or a severe asthma attack. Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to

SYMBICORT. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with SYMBICORT. Lung function (mean forced expiratory volume in 1 second [FEV₁] or morning peak expiratory flow [PEF], beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatique, lassitude, weakness, nausea and vomiting, and hypotension

Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids or SVMBICORT may unmask conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions). Some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

Hypercontisism and Advend Sympassion experimentation of over improvement of respiratory function. Hypercontisism and Advend Symparession Budesonide, a component of SYMBICORT, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of SYMBICORT in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be



NOVEMBER 2014 • CHEST PHYSICIAN

FDA clears glucose testing system for critically ill

or the first time, a blood glucose monitoring system has been cleared for use in critically ill hospitalized patients, the Food and Drug Administration has announced. The device is the Nova StatStrip

Glucose Hospital Meter System, which was cleared for use in 2006 for use in hospitals, but not in critically ill patients.

The expanded use applies to indications using arterial or venous whole

blood, from patients "in all areas of a hospital with various conditions, including: trauma, cancer, sepsis and infection; cardiac, kidney, neurological, obstetric, gynecological, gastroenterological, endocrine, and lung

2

issues; and people recovering from general or cardiothoracic surgery," the statement said.

The system is manufactured by Nova Biomedical.

-Elizabeth Mechatie

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. South rest tarking for during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis)

may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of SYMBICORT should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms. **Drug Interactions With Strong Cytochrome P4263 OA4 Inhibitors** Caution should be exercised when considering the coadministration of SYMBICORT with ketoconazole, and other known

strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saguinavir, along of Dev Immediate (cg., montor), addatast, calanticity of the solution interview in addatast, induction of the solution o

Paradoxical Bronchosposm and Upper Airway Symptoms As with other inhaled medications, SYMBICORT can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, it should be treated immediately with an inhaled, short-acting bronchodilator, SYMBICORT should be discontinued immediately, and alternative therapy should be instituted. Immediate Hypersensitivity Reactions Immediate hypersensitivity reactions may occur after administration of SYMBICORT, as demonstrated by cases of urticaria,

angioedema, rash, and bronchospasm

Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, appiration, nausea, dizziness, fatigue, malaise, and insomnia [see **OVERDOSAGE**]. Therefore, SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol, a component of SYMBICORT, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of formoterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, post menopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of To the second must be an another source of the second seco strongly considered.

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formaterol 4.5, or placebo on BMD was evaluated in a subset of 326 patients (females and males 41 to 88 years of age) with COPD in the 12-month study. BMD evaluations of the hip and lumbar spine regions were conducted at baseline and 52 weeks using dual energy x-ray absorptiometry (DEXA) scans. Mean changes in BMD from baseline to end of treatment were small (mean changes ranged from -0.01 - 0.01 g/cm²). ANCOVA results for total spine and total hip BMD based on the end of treatment time point showed that all geometric LS Mean ratios for the pairwise treatment group comparisons were close to 1, indicating that overall, bone mineral density for total hip and total spine regions for the 12 month time point were stable over the entire treatment period.

Effect on Growth

Crally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving SYMBICORT routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms [see DOSAGE AND ADMINISTRATION and USE IN SPECIFIC POPULATIONS].

Glaucoma and Cataracts Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long-term administration of inhaled corticosteroids, including budesonide, a component of SYMBICORT. Therefore close monitoring is warranted in patients with a change in vision or with history of increased intraocular pressure, glaucoma and/or cataracts

Effects of treatment with SYMBICORT 160/4.5, SYMBICORT 80/4.5, formoterol 4.5, or placebo on development of createrats or treatment with 3 involution 1004-3, 3 involution 304-3, 10 investion 4-3, or placebo or uneventiment or cataracts or gluacoma were evaluated in a subset of 461 patients with COPD in the 12-month study. Ophthalmic examinations were conducted at baseline, 24 weeks, and 52 weeks. There were 26 subjects (6%) with an increase in posterior subcapsular score from baseline to maximum value (>0.7) during the randomized treatment period. Changes in posterior subcapsular scores of >0.7 from baseline to treatment maximum occurred in 11 patients (9.0%) in the SYMBICORT 1604/3.5 group, 4 patients (3.8%) in the SYMBICORT 80/4.5 group, 5 patients (4.2%) in the formoterol group, and 6 patients (5.2%) in the placebo group.

Ecosinophilic Conditions and Churg-Strauss Syndrome In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be aler to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

Coexisting Conditions

VMBICORT, like all medications 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 beta₂-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis

Hypokalemia and Hyperglycemia Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see CLINICAL PHARMACOLOGY in full Prescribing Information (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with SYMBICORT at recommended doses.

ADVERSE REACTIONS

Long-acting belaz-adrenergic agonists, such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled cortico-steroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol [see WARNINGS AND PRECAUTIONS].

Systemic and inhaled corticosteroid use may result in the following: - Candida albicans infection [see WARNINGS AND PRECAUTIONS]

- Canona aniocaris intection [see WARNINGS AND PRECAUTIONS] Pneumonia or lower respiratory tract infections in patients with COPD [see WARNINGS AND PRECAUTIONS] Immunosuppression [see WARNINGS AND PRECAUTIONS] Hypercorticism and adrenal suppression [see WARNINGS AND PRECAUTIONS] Growth effects in pediatric patients [see WARNINGS AND PRECAUTIONS] Glaucoma and cataracts [see WARNINGS AND PRECAUTIONS]

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

The overall safety data in adults and adolescents are based upon 10 active- and placebo-controlled clinical trials in which 3393 patients ages 12 years and older (2052 females and 1341 males) with asthma of varying severity were treated with SYMBICORT by Carbon and Carbon Carbon and Ca The incidence of common adverse events in Table 1 below is based upon pooled data from three 12-week, double-blind

placeb-controlled clinical studies of which and adolescent patients (148 males and 253 females) age 12 years and older were treated with two inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5 twice daily. The SYMBICORT group was composed of mostly Caucasian (84%) patients with a mean age of 38 years, and a mean percent predicted FEV₁ at Was composed of mostly caucasian (64%) patients with a mean age of 36 years, and a mean percent predicted PEV jat baseline of 76 and 68 for the 80/4.5 mog and 160/4.5 mog treatment groups, respectively. Control arms for comparison included two inhalations of budesonide HFA metered dose inhaler (MDI) 80 or 160 mog, formoterol dry powder inhaler (DPI) 4.5 mog, or placebo (MDI and DPI) twice daily. Table 1 includes all adverse events that occurred at a incidence of 2-3% in any one SYMBICORT group and more commonly than in the placebo group with twice-daily obsing. In considering these data, the increased average duration of patient exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for an imbalance of treatment duration.

Adverse reactions occurring at an incidence of >3% and more commonly than placebo in the SYMBICORT groups: pooled data from three 12-week, double-blind, placebo-controlled clinical asthma trials in patients Table 1 groups: pooled data 12 years and older

Treatment*	SYMBICORT		Budesonide		Formoterol	Placebo	
Adverse Event	80/4.5 mcg N = 277 %	160/4.5 mcg N =124 %	80 mcg N =121 %	160 mcg N = 109 %	4.5 mcg N = 237 %	N = 400 %	
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0	
Headache	6.5	11.3	11.6	12.8	8.9	6.5	
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8	
Pharyngolaryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8	
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8	
Influenza	3.2	2.4	6.6	0.9	3.0	1.3	
Back pain	3.2	1.6	2.5	5.5	2.1	0.8	
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0	
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8	
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0	
Oral Candidiasis	1.4	3.2	0	0	0	0.8	
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9	

All treatments were administered as two inhalations twice daily Long-term safety - asthma clinical trials in patients 12 years and older

Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to 1 year at doses up to 200/36 mc/34/4 (64/18 mcg twice daily), revealed neither 2 period and a period of the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to 1 year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA-axis

Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The incidence of common adverse events in Table 2 below is based upon pooled data from two double-blind, placebo-controlled clinical studies (6 and 12 months in duration) in which 771 adult COPD patients (496 males and 275 females) 40 years of age and older were treated with SYMBICORT 160/4.5, two inhalations twice daily. Of these patients 651 were treated for 6 months and 366 were treated for 12 months. The SYMBICORT group was composed of mostly Caucasian (93% Table 0 of months are age of 63 years, and a man percent predicted FEV₄ at baseline of 330. Control arms for comparison included two inhalations of budesonide HFA (MDI) 160 mcg, formoterol (DPI) 4.5 mcg or placebo (MDI and DPI) twice daily. Table 2 includes all adverse events that occurred at an incidence of ≥3% in the SYMBICORT group and more commonly than increased and the second sec in the placebo group. In considering these data, the increased average duration of patient exposure to SYMBICORT should be taken into account, as incidences are not adjusted for an imbalance of treatment duration

Table 2 Adverse reactions occurring at an incidence of ≥3% and more commonly than placebo in the

Treatment*	SYMBICORT	Budesonide	Formoterol	Placebo
	160/4.5 mcg N = 771	160 mcg N = 275	4.5 mcg N = 779	N = 781
Adverse Event	%	%	%	%
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Upper respiratory tract				
infection viral	3.5	1.8	3.6	2.7
Average Duration of				
Exposure (days)	255.2	157.1	240.3	223.7

Lung infections other than pneumonia (mostly bronchitis) occurred in a greater percentage of subjects treated with SYMBICORT 160/4.5 compared with placebo (7.9% vs. 5.1%, respectively). There were no clinically important or unexpected patterns of abnormalities observed for up to 1 year in chemistry, haematology, ECG, ECG (Holter) monitoring, HPA-axis, bone mineral density and ophthalmology assessments.

Postmorketing Experience The following adverse reactions have been reported during post-approval use of SYMBICORT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with SYMBICORT.

Cardiac disorders: angina pectoris, tachycardia, atrial and ventricular tachyarrhythmias, atrial fibrillation, extrasystoles palpitations

Endocrine disorders: hypercorticism, growth velocity reduction in pediatric patients

Eye disorders: cataract, glaucoma, increased intraocular pressure

Gastrointestinal disorders: oropharyngeal candidiasis, nausea Immune system disorders: immediate and delayed hypersensitivity reactions, such as anaphylactic reaction, angioedema bronchospasm, urticaria, exanthema, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia Musculoskeletal, connective tissue, and bone disorders: muscle cramps

Nervous system disorders: tremor dizziness

Psychiatric disorders: behavior disturbances, sleep disturbances, nervousness, agitation, depression, restlessness Respiratory, thoracic, and mediastinal disorders: dysphonia, cough, throat irritation

Skin and subcutaneous tissue disorders: skin bruising

Vascular disorders: hypotension, hypertension

DRUG INTERACTIONS

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta₂-agonists, intranasal controcsteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse reactions. No formal drug interaction studies have been performed with SYMBICORT.

Industry ties may bias neuraminidase inhibitor reviews

BY MARY ANN MOON Frontline Medical News

n systematic reviews of research on neuraminidase inhibitors for either prevention or treatment of influenza, authors who had ties to drug manufacturers were much more likely to present the evidence as favorable and to recommend the drugs than were authors who had no such conflicts of interest, according to a

report published in Annals of Internal Medicine.

"Reviewers with such conflicts of interest were also less likely to address issues with the underlying primary clinical evidence, such as pub-

SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of CYP3A4 may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the metabolism of the systemic exposure to budesonide increased. the coadministration of SYMBICORT with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) [see WARNINGS AND PRECAUTIONS

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricvclic SYMBICORT, should be administed on more than a standard being active that more than a standard on any operation of the standard on a standard adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the sof beta adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution. Diuretics

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

USE IN SPECIFIC POPULATIONS

USE IN SPECIFIC FOR OCHINESE Pregnancy Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled studies of SYMBICORT in pregnant women. SYMBICORT was teratogenic and embryocial in rats. Budesonide alone was teratogenic and embryocidal in rats and rabbits, but not in humans at therapeutic doses. Formoterol fumarate alone was teratogenic in rats and rabbits. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a reproduction study in rats, budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/7 and 1/3, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis produced umbilical hernia. No teratogenic or embryocidal effects were detected with budesonide combined with formoterol fumarate by the inhalation route at doses approximately 1/32 and 1/16, respectively, the maximum recommended human daily inhalation dose on a mg/m² basis

Budesonide

Studies of pregnant women have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry, Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital bit megas, regist, regist, regist, or congenital manomators, one calculate of the second seco to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal to make bucksome, the number of mains both with oblication between statistics was similar to the expected humber in the normal population (4 children vs.3, stepsective)). These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled

budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budes-onide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%). Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses in rabbits less than

the maximum recommended human daily inhalation dose on a mcg/m² basis and in rats at doses approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m² basis. In another study in rats, no teratogenic or ambryckial effects were seen at inhalation doses up to 3 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans

Formoterol

Formoterol fumarate has been shown to be teratogenic, embryocidal, to increase pup loss at birth and during lactation, and to decrease pup weights in rats when given at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Umbilican Hernia was observed in rat fetuses at oral doses 1400 times and greater the maximum recommended human daily inhalation dose on a mcg/m² basis. Brachygnathia was observed in rat fetuses at an dose at an expression of the second second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. The second basis at an expression of the second basis at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis at an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis at an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis at an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis at an expression of the second basis. Brachygnathia was observed in rat fetuses at an an expression of the second basis at a second basis. Brachygnathia at a second basis at a second basis at a second basis at a se oral dose 7000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. Pregnancy was prolonged that user food international recommended numan daily inhalation does on a mog/m² basis. In another study in rats, no teratogenic effects were seen at inhalation does up to 500 times the maximum recommended human daily inhalation does on a mcg/m² basis.

Subcassular cysts on the liver were observed in rabbit fetuses at an oral dose 54,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis. No teratogenic effects were observed at oral doses up to 3200 times the maximum recommended human daily inhalation dose on a mcg/m² basis.

Nonteratogenic Effects Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Labor and Delivery There are no well-controlled human studies that have investigated the effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother. Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral does of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother [see CLINICAL PHARMACOLOGY, Pharmacokinetics in full Prescribing Information (12.3)]. For SYMBICORT, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

Pediatric Use

Safety and effectiveness of SYMBICORT in asthma natients 12 years of age and older have been established in studies up Sately and electronices of or Molecorn in asimilar parents regression age and other have been escatarised in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily [see **CLINICAL STUDIES** in full Prescribing Information (14.1)]. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older. The safety and effectiveness of SYMBICORT in asthma patients 6 to <12 years of age has not been established Overall 1447 asthma patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that bserved in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid evolution of the Acar Suppression, suggesting that growth velocity is a more sensitive indicator of systemic conclusion controls exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn fron this study may be confounded or and clinicell reactive will proceed that similar growth reactives, conclusions drawn non this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or addesent on any controsteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBIOCHT, each patient should be titrated to the lowest strength that effectively controls his/her asthma [see DOSAGE AND ADMINISTRATION]. Geriatric Use

Of the total number of patients in asthma clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom 25 were 75 years of age or older.

In the COPD studies of 6 to 12 months duration, 349 patients treated with SYMBICORT 160/4 5 twice daily were 65 years of In the COPD studies of 60 to monthly duration, one patients treated with a findicion from 3,5 whice during were do years of the and block. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

As with other products containing beta₂-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric

patients is warranted. Hepatic Impairment

Formal pharmacokinetic studies using SYMBICORT have not been conducted in patients with hepatic impairment. However since both budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism, impairment of live should be closely monitored.

Renal Impairment Formal phar

nacokinetic studies using SYMBICORT have not been conducted in patients with renal impairment. OVERDOSAGE

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individua components described below apply to SYMBICORT. In pharmacokinetic studies, single does of 960/54 mcg (12 actuations of SYMBICORT 80/4.5) and 1280/36 mcg (8 actuations of 160/4.5), were administered to patients with COPD. A total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single does to both healthy subjects and patients with asthma. In a long-term active-controlled safety study in asthma patients, SYMBICORT 160/4.5 was administered for up to 12 months at doses up to twice the highest recommended daily dose. There were no clinically significant adverse reaction observed in any of these studies.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarh, redness oi intact skin, abdominal respiration, vomiting, and salivation, in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation doses of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths occurred in doos given a combination of budesonide and formoterol at the acute inhalation doses of 732 and 22 mcg/kg, respectively (approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m² basis).

Budesonide

The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur [see WARNINGS AND PRECAUTIONS]. Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect (27.78) in the plasma consol response to a C-noil matching of Compared with places (47.78). The corresponding energy of 10 mg prediction (47.78) as 35% reduction in the plasma corrisol response to ACTH. In mice, the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended humar

daily inhalation dose on a mcg/m² basis). In rats, there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m² basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 1300 tinks the maximum recommended human daily inhalation dose on a mcg/m² basis).

Formoterol

An overdose of formoterol would likely lead to an exaggeration of effects that are typical for beta₂-agonists: seizures angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremon applications, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. No clinically significant adverse reactions were seen when formoterol was delivered to adult patients with acute bronchoconstriction at a dose of 90 mcg/day over 3 hours or to stable asthmatics 3 times a day at a total dose of 54 mcg/day for 3 days. Treatment of formoterol overdosage consists of discontinuation of the medication 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 medication can produce bronchospasm. There is insufficient evidence to determine if dialysis

is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m² basis). In rats, the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m² basis). Maximum nonlethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m² basis)

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lication bias and the lack of access to comprehensive study data," said Adam G. Dunn, Ph.D., of the Centre for Health Informatics, University of New South Wales, Sydney, and his associates (Ann. Intern. Med. 2014 Oct.6 [doi:10.7326/M14-0933]).

The findings suggest that "further measures may be necessary to ensure that industry collaborations do not compromise the scientific evidence," the investigators noted.

"If the benefits of neuraminidase inhibitors are eventually found to have been inflated, millions of patients will have been unnecessarily exposed to drugs that may be of little or no benefit," the researchers added.

Dr. Dunn and his colleagues observed that reviews of neuraminidase inhibitors had widely divergent conclusions, with some strongly endorsing the agents as influenza prophylaxis or treatment, while others questioned the drugs' safety and efficacy.

To examine whether industry influence may have contributed to these inconsistent conclusions, the investigators analyzed 26 systematic reviews. Thirteen assessed prophylaxis, and 24 assessed treatment; so, there were 37 distinct assessments. Seven of those were Cochrane analyses.

Two of the investigators read redacted copies of the reviews and rated them as favorable or unfavorable toward the use of neuraminidase inhibitors. Those copies showed no identifying information for the authors and no journal name or formatting clues. The agreement between the two investigators was "strong," at 86%.

At the same time, Dr. Dunn and his associates searched for all the financial conflicts of interest for all the authors of these reviews, paying special attention to ties to the pharmaceutical companies that made the neuraminidase inhibitors under review. To do so, they went beyond the affiliations and funding listed in the systematic reviews, examining the authors' personal and institutional websites, as well as disclosure lists provided by GlaxoSmithKline and Roche. They also performed Web searches combining the authors' names, drug names, and manufacturers' names.

Reviewers who had ties to the pharmaceutical industry rated neuraminidase inhibitors favorably in 88% (seven of eight) systematic reviews. In contrast, reviewers who had no such ties rated the drugs favorably Continued on following page

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Continued from previous page

in only 17% (5 of 29) of systematic reviews. That pattern persisted when prophylaxis and treatment were assessed separately.

Regarding prophylaxis, 100% (2 of 2) of the reviews with financial conflicts of interest were favorable, compared with only 9% (1 of 11) of those without conflicts of interest. Regarding treatment, 83% (5 of 6) of the reviews with financial conflicts of interest were favorable, compared with only 22% (4 of 18) of those without conflicts of interest.

In addition, reviewers who had ties to the pharmaceutical industry were

VIEW ON THE NEWS

Dr. Daniel Ouellette, FCCP, comments: A couple of decades ago, I received a stethoscope from a pharmaceutical compa-

ny. The rep arrived one day in my office, and simply gave me a stethoscope, which prominently displayed the name of an antibiotic and



the company. I kept the stethoscope in my office as a "spare," and bragged to colleagues that I wasn't biased, because I never prescribed the drug in question. None of us think that we are biased by industry gifts and payment for services. The fact is: We are.

Physicians who are the authors of systematic reviews concerning the use of neuraminidase inhibitors for the treatment of influenza were dramatically more likely to support use if they had industry ties. Investigators had to search authors' websites and curriculum vitae, and industry "sunshine" websites, to find relationships, as authors did not always report such connections. All of us use the information from systematic reviews and guidelines to inform our practice. Can we depend on this information? Only if we as authors are scrupulous about avoiding conflicts of interest and if we correctly report our potential conflicts.

Also required: Developers of evidence-based medicine tools must perform careful conflict of interest assessments of authors. less likely to include information about publication bias in their reports (14%, or only 1 of 7), compared with reviewers who had no such ties (79%, or 15 of 19), Dr. Dunn and his associates said.

The study findings indicate that financial conflicts of interest "are associated with product assessments favorable to the sponsors involved," the authors asserted.

Factors that may contribute to biased conclusions include "the design of the review, the patient populations and outcomes assessed, the selective inclusion of primary evidence, [and] the critical appraisal of evidence quality and provenance," the investigators noted. In addition, "the tone, emphasis, and interpretation provided by the authors may also influence the message that is conveyed," they said.

The Australian National Health and Medical Research Council funded the study. Dr. Dunn and his associates reported having no financial conflicts of interest.

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SCHEST Physician

Cases of smoking-related conditions top 14 million

BY AMY KARON Frontline Medical News

igarette smoking caused at least 14 million cases of major medical conditions among U.S. adults in 2009, investigators reported in JAMA Internal Medicine.

The statistic substantially exceeds a 2000 estimate by the Centers for Disease Control and Prevention of 12.7 million smoking-related conditions among 8.6 million individuals, said Brian L. Rostron, Ph.D., at the U.S. Food and Drug Administration, Silver Spring, Md., and his associates.

The discrepancy most likely stems from the fact that respondents in national health surveys tend to underreport chronic obstructive pulmonary disease (COPD), the leading medical consequence of smoking, the researchers said.

Using spirometry data, they estimated more than 7.4 million cases of COPD attributable to smoking in 2009, which was 70% higher than past statistics based on self-reported data, they said (JAMA Intern. Med. 2014 Oct. 13 [doi:10.1001/jamainternmed.2014.5219]).

For the study, the researchers used data from the 2009 U.S. Census Bu-

reau, the 2006-2012 National Health Interview Survey, and the National Health and Nutrition Examination Survey to calculate the population-attributable risk of major smoking-related conditions among U.S. adults aged 35 years and older. Besides

of 6.9 million adults in the United States with at least one major medical condition secondary to smoking (95% confidence interval, 6.5-7.4 million), with a total of 10.9 million conditions identified (95% CI, 10.3-11.5 million), the researchers said.



Because many respondents to health surveys underreport COPD, previous CDC estimates of smoking-related illness were too low, according to a new study.

COPD, these conditions included diabetes mellitus, heart attacks, cancer, and stroke.

This approach yielded an estimate

To better estimate the burden of COPD secondary to smoking, the investigators then used self-reported and spirometry data from the National Health and Nutrition Examination Survey. This analysis identified 14 million smoking-attributable conditions overall, including more than 7.4 million cases of COPD, they said. Notably, COPD was 3.78 times more common among current female smokers than never smokers, and four times more common among male smokers than never smokers, they said.

The results are "generally conservative, owing to the existence of other diseases and medical events that were not included in these estimates," the researchers wrote, adding that "the International Agency for Research on Cancer has concluded, for example, that ovarian cancer, specifically mucinous tumors, is caused by smoking." Current estimates also do not capture the prevalence of cardiovascular surgeries, congestive heart failure, peripheral arterial disease, rheumatoid arthritis, and macular degeneration attributable to smoking, said the investigators.

Descriptions of medical diagnoses were self-reported and therefore might not always be accurate, Dr. Rostron and associates noted. They reported no funding sources or conflicts of interest.

FDA panel: Keep Chantix boxed warning ... for now

BY ELIZABETH MECHCATIE Frontline Medical News

SILVER SPRING, MD. – The boxed warning about the risk of serious neuropsychiatric effects linked to the smoking cessation drug varenicline should remain on the drug's label, and the need for the warning can be reevaluated when results of a postmarketing safety study are available next year,

the majority of a Food and Drug Administration advisory panel decided.

At a joint meeting of the FDA's Psychopharmacologic Drugs and the Drug Safety and Risk Management Advisory committees, 11 of the 18 panelists voted to retain the boxed warning about neuropsychiatric symptoms and suicidality.



Pfizer, which manufactures the nicotinic receptor partial agonist in a tablet formulation as Chantix, is doing a prospective, randomized, double-blind study comparing neuropsychiatric events in 8,000 smokers, with and without a psychiatric history, treated with varenicline, nicotine replacement therapy, bupropion, or placebo. Results are expected in 2015. The company maintained that the boxed warning is no longer justified and can be put in the warnings and precautions section, based on analyses of observational studies and randomized clinical trials that were submitted to the FDA earlier this year.

The warning states that the serious events include but "are not limited to" depression, suicidal ideation, suicide attempts, and completed suicides; and that some cases "may have been complicated by the symptoms of nicotine

Removal of the warning might be seen as an 'endorsement of safety and that has not been demonstrated.'

DR. PERRONE

withdrawal in patients who stopped smoking." The boxed warning is used for this drug because there is a "serious adverse reaction that can be prevented or reduced in frequency or severity," the FDA said.

The panelists cited weaknesses in the observational studies and the meta-analysis.

Six panelists voted to modify the language in the warning, and most recommended that lines about the health benefits of quitting smoking be removed, citing a promotional tone. Several panelists recommended adding sleep disruption and disorders, and recognized adverse events of the drugs.

Dr. Jeanmarie Perrone, director of medical toxicology in the emergency medicine department at the University of Pennsylvania, Philadelphia, who voted to retain the warning, said there was biologic plausibility for these events. Removal of the warning might be seen as "an endorsement of safety and that has not been demonstrated," she said.

The FDA usually follows the recommendations of its advisory panels, which are not binding. Serious adverse events should be reported to MedWatch at www.fda.gov/Safety/MedWatch/default.htm.

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22 PULMONARY MEDICINE

Pneumonia readmissions dived under QI initiative

BY SHARON WORCESTER Frontline Medical News

AUSTIN, TEX. – A multidisciplinary intervention, including implementation of a diagnostic scoring system and daily interdepartmental meetings to review cases, significantly decreased readmission rates for patients at a tertiary care center who were discharged with a diagnosis of pneumonia.

VITALS

Key clinical point: A scoring system and multidisciplinary effort improved pneumonia patient readmission rates and diagnostic accuracy.

Major finding: All-cause and pneumonia-related readmission rates declined from 20.7% to 13.2%, and from 10.5% to 3%, respectively.

Data source: A retrospective study of the charts of 463 patients.

Disclosures: Dr. Hussein reported having no disclosures.

From November 2012 to January 2013 – a 3-month period after implementation of the quality improvement (QI) initiative - the allcause readmission rates among 227 patients discharged with a diagnosis of pneumonia declined by 7.5 percentage points, compared with the all-cause readmission rates among 236 patients discharged during the same period in the prior year, before implementation of the initiative (from 20.7% to 13.2%), Dr. Hussein Hussein, a fellow at the University of Oklahoma Health Sciences Čenter, Oklahoma City, reported at CHEST 2014.

A similar reduction was seen for pneumonia-related readmissions, which declined from 10.5% to 3% during the same period, said Dr. Hussein, who was with Yale New Haven (Conn.) Hospital, at the time the research was conducted.

Further, after implementation of the scoring system - a modified Clinical Pulmonary Infection Score (MCPIS) calculated based on patient temperature, white blood cell count, sputum cultures, oxygen requirements, and radiographic appearance, which was administered at admission and again at 32 hours - the accuracy of pneumonia diagnoses appeared to improve; the mean MCPIS scores among patients with a discharge diagnosis of pneumonia increased significantly after implementation (from 4 to 6); the proportion of patients considered unlikely to have pneumonia decreased from 42.6% to 3.6%; the proportion considered to probably have pneumonia decreased from 31.9% to 17.9%; and the number deemed likely to have pneumonia increased from 25.5% to 78.6%.

All of the changes were statistically significant, and the improved accuracy of diagnosis was likely a result of provider education that led to increased use of sputum cultures, Dr. Hussein noted.

Pneumonia is the second most common discharge diagnosis among Medicare beneficiaries, and nearly 20% of these patients are readmitted within 30 days at a cost exceeding

Approximately 50% of individuals with narcolepsy are undiagnosed.¹

ALL THE TIME

CATAPLEXY HYPNAGOGIC HALLUCINATIONS EXCESSIVE DAYTIME SLEEPINESS SLEEP PARALYSIS SLEEP DISRUPTION

Narcolepsy symptoms may be lurking beneath the surface.

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\$17 billion annually.

"This is why the Centers for Medicare & Medicaid Services is penalizing poor-performing hospitals with high rates of readmission," he said.

The MCPIS was implemented in 2012 as a quality improvement tool. Based on the scores, patients were categorized as unlikely to have pneumonia (score of 3 or less), probably having pneumonia (score of 4-5), and likely to have pneumonia (score of 6 or greater). The daily meetings during which patients admitted with pneumonia were reviewed involved participation of physicians from different medical divisions and representatives from nursing, social work,

and continuing care.

The primary goal of these rounds was to ensure timely follow-up after discharge, Dr. Hussein explained, adding that if the diagnosis was felt to be incorrect, the case was discussed with the team that was caring for the patient.

To assess the effects of this inter-

To identify the symptoms of narcolepsy,

LOOK DEEPER



Hypnagogic Hallucinations: Vivid dream-like experiences that occur during the

Cataplexy: A sudden, temporary loss of muscle tone triggered by strong emotions^{1,2}

transitions between wake and sleep^{1,2}

Excessive Daytime Sleepiness: The inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep²

Sleep Paralysis: The temporary inability to move or speak while falling asleep or waking up²

Sleep Disruption: The interruption of sleep by frequent awakenings^{1,2}

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

Narcolepsy Is a Chronic, Life-Disrupting Neurologic Disorder^{2,3}

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.¹⁻⁴

Narcolepsy Is Underdiagnosed

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

Narcolepsy Symptoms Can Be Difficult to Recognize

Narcolepsy symptoms may overlap with those of other conditions, such as obstructive sleep apnea and depression.¹² The initial and presenting symptom is typically some manifestation of excessive daytime sleepiness such as tiredness, fatigue, difficulty concentrating, or mood changes.^{12,5} 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

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



vention, he and his colleagues conducted a retrospective chart review of all patients discharged with a diagnosis of pneumonia during each of the two assessment periods.

Vaccine slashes the odds of flu hospitalizations

PHILADELPHIA – Receiving a flu shot cut the odds of influenza hospitalizations by 56% among older adults during the 2010-1011 flu season, surveillance data show.

Vaccine effectiveness was consistent across all age groups, even among those aged 75 years or older.

"Continued emphasis on the importance of influenza vaccination among older adults is crucial," Dr. Fiona Havers said at ID Week.

She reported on 364 adults, aged 50 years and older, who received a flu shot at least 14 days prior to hospital admission for laboratory-confirmed influenza during the 2010-2011 season. Cases were admitted to one of 11 sites participating in the Emerging Infections Program, now Flu-Surv-Net, and were matched by age and county to 773 controls.

Cases were significantly more likely than were controls to be of nonwhite race (31% vs. 15%), to be Hispanic (7% vs. 2%), to have an annual income less than \$35,000 (52% vs. 33%), to have high school or lower-level education (44% vs. 27%), and to have at least two chronic conditions (72% vs. 36%).

Estimates of influenza vaccine effectiveness in preventing hospitalization was 33% for all ages, 33% for ages 50-64 years, 45% for ages 65-74 years, and 21% for those 75 years and older, reported Dr. Havers of the influenza division of the Centers for Disease Control and Prevention.

After adjustment for age, gender, race/ethnicity, income, education, recent hospitalization, functional status, and chronic medical conditions, vaccine effectiveness estimates were 56%, 64%, 61%, and 57%, respectively.

The investigators also looked at influenza subtype and found that after adjustment, vaccination was associated with a significant reduction in the risk of hospitalizations for influenza A H3N2 (51%) and influenza B (95%).

ID Week comprises the annual meetings of the Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, HIV Medicine Association, and Pediatric Infectious Diseases Society. –Patrice Wendling <text><text><text>

Indication

- ANORO ELLIPTA is a combination anticholinergic/long-acting beta₂-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
- ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Important Safety Information for ANORO ELLIPTA

WARNING: ASTHMA-RELATED DEATH

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.
- ANORO ELLIPTA should not be used for the relief of acute symptoms, ie, as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.
- 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) FEV₁ by 167 mL vs placebo (*P*<0.001) at Day 169¹

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) FEV₁ at Day 169 (defined as the mean of the FEV₁ values obtained 23 and 24 hours after dosing on Day 168).¹

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

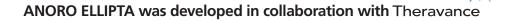
- The most common adverse reactions (≥1% and more common than placebo) reported in four 6-month clinical trials with ANORO ELLIPTA (and placebo) were: pharyngitis, 2% (<1%); sinusitis, 1% (<1%); lower respiratory tract infection, 1% (<1%); constipation, 1% (<1%); diarrhea, 2% (1%); pain in extremity,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

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 umeclidinium/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[™] (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder)



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 beta₂-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 beta₂-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 beta₂-agonist. When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta₂-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 beta₂-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta₂-agonist becomes less effective; or the patient needs more short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of 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 Beta₂-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 beta₂-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.

BRIEF SUMMARY 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 beta₂-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.

<u>6-Month Trials</u>: 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 activecontrolled 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 (FEV₁) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV₁/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%). Subjects received 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.

<u>12-Month Trial:</u> 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, troleandomycin, 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 beta₂-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-potassiumsparing 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

<u>Teratogenic Effects:</u> 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/m² 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). *Vilanterol:* fects at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m² 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.

<u>Nonteratogenic Effects:</u> <u>Umeclidinium</u>: 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/m² 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

<u>ANORO ELLIPTA</u>: 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.

<u>Umeclidinium</u>: 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.

<u>Vilanterol</u>: It is not known whether vilanterol is excreted in human breast milk. However, other beta₂-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_{max} or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed *[see Clinical Pharmacology (12.3) of full Prescribing Information].*

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 uneclidinium 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

<u>ANORO ELLIPTA</u>: 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. <u>Umeclidinium</u>: 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).

<u>Vilanterol:</u> 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/m² basis).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). <u>Asthma-Related Death</u>: 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. <u>Not for Acute Symptoms</u>: 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.

<u>Do Not Use Additional Long-Acting Beta</u>, <u>Agonists</u>: 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 beta₂-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

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

<u>Risks Associated With Beta-Agonist Therapy:</u> Inform patients of adverse effects associated with beta₂-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.

<u>Worsening of Narrow-Angle Glaucoma</u>: 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.

<u>Worsening of Urinary Retention</u>: 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.



Research Triangle Park, NC 27709

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ANR:1BRS

Malpractice premiums remained flat in 2014

BY ALICIA GALLEGOS Frontline Medical News

alpractice premiums stayed mostly the same in 2014, with 65% of liability insurance rates steady nationwide, according to the Medical Liability Monitor's annual survey.

Trends of slow lawsuit frequency and low plaintiff payouts contribute to the steady market, said Chad C. Karls, editor of the 2014 Annual Rate Survey and a principal and consulting

VIEW ON THE NEWS

Dr. Lary Robinson, FCCP, com-

ments: One of the most painful aspects of practicing medicine is paying malpractice insurance premiums. But based on the Medical Liability Monitor's 2014 annual survey, some sunshine has crept into this field, with the finding of flat malpractice premiums nationwide.

States such as Nevada credit tort reform legislation with nonecoactuary for Milliman in Brookfield, Wis.

There are large verdicts, "but when we take it across all claims, the vast majority don't have a verdict attached to them," Mr. Karls said in an interview. "The vast majority get settled."

But unchanging insurance rates can mean misery or relief depending on practice locations. Internists in southern Florida will pay a high of \$47,707 for malpractice insurance this year, while those in South Dakota will pay \$3,697. Ob.gyns. in the New

nomic damage limits as the reason

lawsuits are down and premiums are flat. Also, the consolidation of medical practices with better risk management may have had a positive effect. Still to be determined is the effect of the Affordable Care Act on the frequency of malpractice lawsuits with

increasingly more patients getting care from the same number of physicians.

York counties of Nassau and Suffolk will pay \$214,999 in premiums, but in Central California, they will pay \$16,240. General surgeons in southern Florida will dish out \$190,829 in 2014, while Wisconsin surgeons will pay \$10,868.

Premiums increased in some areas. Indiana physicians saw the highest increase at 4.5%.

Nevada doctors saw a 34.8% decrease, the largest drop. Nevada's rate decline is not surprising, said Dr. Warren Volker, trustee-at-large for the Clark County (Nev.) Medical Society and chair of Premiere Physician Insurance Company in Nevada. Doctors there have seen a stable medical liability climate for the last decade, he said. "Our premiums have gone down dramatically, across the board," Dr. Volker said in an interview. He attributed the declines to tort reform in 2002, including a \$350,000 noneconomic damages cap in medical malpractice cases. Since then, the number of lawsuits has gone down and competition among liability insurers has increased, he said.

Legal reforms such as Nevada's have contributed to the overall decrease in lawsuits and payout severity across the country, Mr. Karls said. Patient safety initiatives and better risk management within medical practices also have an impact.

Industry analysts have not seen an impact by the Affordable Care Act on malpractice insurance rates, Mr. Karls said. There might be fewer claims if the ACA results in proactive approaches to medical errors and less acute care, but in the short term, more patients covered under the ACA could mean a rise in lawsuits and premiums.

Dr. Volker said he expects the trend of practice mergers and acquisitions to continue as more physicians seek to escape high premium costs and regulatory burdens. "What you're going to see in the hotbeds is more migration," said Dr. Volker, who practices in Nevada, California, Florida, and Arizona. "More doctors [will be] giving up their individual practices and joining larger groups.'

The MLM survey, published in October, gathered July 1 data from major malpractice insurers and examined rates for mature, claims-made policies with \$1 million/\$3 million limits for internists, general surgeons, and ob.gyns.

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- tions Development of leadership skills in the pulmonary and critical care fields
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- practice Presentations for self-study stations and case-based interactive discussions



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All topic submitters and all proposed faculty will be required to complete financial disclosures before the topic submission will be final. Learn more at chestmeeting.chestnet.org.

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Survey: Many physicians plan to reduce their workload

BY ALICIA GALLEGOS Frontline Medical News

early 45% of physicians plan to cut back on seeing patients, to take on fewer patients, or to retire within the next 3 years.

Increased workloads, regulatory burdens, and changes to the health care system are drivers of the anticipated career moves, according to a survey of 20,088 physicians commissioned by the Physicians Foundation, a nonprofit research organization.

The 2014 Survey of America's Physicians: Practice Patterns and Perspectives, released by Merritt Hawkins, is based on responses from physicians nationwide from March to June of 2014. The survey found 81% of physicians described themselves as overextended or at full capacity, up from 75% in 2012. Within the next 1-3 years, 18% of doctors said they plan to reduce their hours, 10% plan to seek a nonclinical job, 9% will retire, and 8% plan to reduce the number of patients seen. Also, 39% said they will accelerate their retirement plans because of changes in the health care system.

Twenty-nine percent of respondents gave the Affordable Care Act a C grade as a vehicle for health reform; 21% gave ita D, and 25% issued an F. Just 4% gave the law an A; 22% gave it a B.

Dr. Walker Ray, vice president of the Physicians Foundation, said the results suggest a looming physician

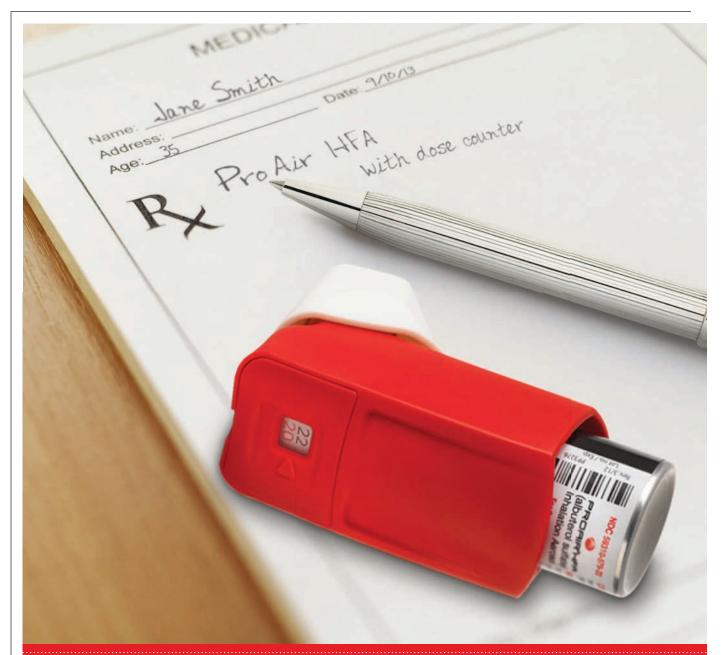
VIEW ON THE NEWS

Dr. James A.L. Mathers Jr., FCCP, comments: Most of the numbers cited here are in the ballpark with similar surveys and reflect the

impact of policies that limited medical school enrollment and funding for postgraduate training in the 1990s and early 2000s. Statistics show



that about 42% of practicing physicians in this country are older than 55 and about 21% are over 65. The HITEC Act and the ACA increased CMS control over Medicare spending but also substantially increased the administrative burden on physicians. This increased burden, both in the costs and time commitment of maintaining a practice, is taking its toll. shortage and decreased quality care. Electronic medical records have been adopted by 85% of physicians, up from 70% in 2012, the survey found. But 46% of respondents said that EMRs have reduced their efficiency, while 24% say the systems have improved their efficiency. Doctors worked an average of 53 hours a week in 2014, the same number of hours reported in 2012. Physicians spent an average of 20% of their time on nonclinical paperwork in 2014. Fifty-three percent were hospital or medical group employees, up from 44% in 2012 and 38% in 2008. In 2014, 35% said they were independent practice owners, down from 49% in 2012.



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CHEST Foundation targets cancer, COPD awareness

ovember is National Awareness Month for lung cancer and COPD, two of the leading causes of death in the United States. In observance of the month, CHEST Foundation, with grant support, launched three unique campaigns to raise awareness and to educate people living with lung cancer or COPD.

'Lung Cancer Care: A Team Approach' reinforces importance of multidisciplinary team for optimal lung cancer care

www.LungCancerTeam.com With support from Genentech, a member of the Roche Group, this campaign aims to encourage pulmonologists to engage other lung cancer specialists in providing multidisciplinary, patient-centered care.



"Pulmonologists play a key role in diagnosing, staging, and treating patients with lung cancer," said CHEST Medical Director Mark J. Rosen, MD, Master FCCP. 'As early intervention improves survival, upon patient diagnosis, we encourage pulmonologists to collaborate with oncologists, thoracic surgeons,

and other lung cancer specialists on multidisciplinary efforts that may result in better patient outcomes."

'Tome Un Respiro' provides Spanish-language COPD resources www.TomeUnRespiro.com

Sunovion Pharmaceuticals Inc. is supporting CHEST Foundation's



Spanish-language COPD campaign, "Tome Un Respiro" ("Take a Breath") to reach the US Hispanic community. The foundation's website now features Spanish-language content about COPD symptoms, causes, testing and diagnosis, treatment, and other resources.

"We saw a need to address the lack of Spanish-language COPD resources available to the Hispanic community," said Henry McMillan, Director for Respiratory Marketing at Sunovion Pharmaceuticals Inc. "We were honored to support CHEST to provide COPD information to the

Hispanic community through this campaign."

'Live Well' advocates for healthy behaviors in COPD population

www.TakeControlLiveWell.com "You Can Live Well With COPD" is the overarching message of this campaign made possible

through a charitable grant from AstraZeneca. The "Take Control. Live Well." message encourages people living with COPD to adopt healthy lifestyle behav-

iors for better management of their illness and to improve their quality of life. Clinicians can now find resources on the website for sharing with their COPD patients, including a "COPD Lifestyle Management Tool" and "Living Well With COPD" booklet.

The campaigns will continue throughout November targeting health-care providers, patients, family



members, and caregivers. Visit chestnet.org/ Foundation and follow us on Twitter. Facebook, and LinkedIn for more information. All three campaigns support the foundation's

goal to make an impact on world health, one community at a time.



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Echocardiography June 4-6 Celebration of Pediatric Pulmonology

June 12-13 Comprehensive Pleural Procedures

June 18-20 Difficult Airway Management

Code acute bronchiolitis using ICD-10-CM

Time is short to learn the new diagnosis coding system.

BY RHONDA BUCKHOLTZ, CPC, VICE PRESIDENT OF ICD-**10 TRAINING AND EDUCATION** AT AAPC

ffective October 1, 2015, we face a massive change: the implementation of ICD-10-CM and ICD-10-PCS. Chest coders must learn a completely new diagnosis coding system. To illustrate the documentation specificity necessary to code in ICD-10, consider the following ICD-10 coding snapshot using a case of an infant diagnosed with acute bronchiolitis.

Chief complaint: Increased work of breathing

A 3-month-old girl was brought to the ED by her mother. She became ill about a week ago. Her mother says she was using the vaporizer and thinks it helped. The patient's cough gradually worsened, and 3 days ago it increased significantly, with increased congestion. Two days ago, she was brought to the ED and was given levalbuterol, 2 puffs every 4 to 6 h, but her mother states this did not help. Today, she had difficulty breathing.

She gagged and vomited with feedings, had a temperature of 101°, and mother has brought her back. ROS: Otherwise negative. Medications: Levalbuterol Family history: Mother, father, and brother all have asthma. Father smokes in the presence of child.

To illustrate the documentation specificity necessary to code in ICD-10, consider this snapshot using a case of an infant diagnosed with acute bronchiolitis.

Physical examination: Normal vital signs, but patient fussy. Respiratory rate around 36-45 breaths per minute; oxygen saturation, 100% on oxygen at 0.5 L/min; 89% breathing room air. HEENT: normal. Chest: Symmetrical expansion and retractions. Lungs: diffuse crackles bilaterally, some wheezing, no rhonchi.

Cardio: 2/6 systolic ejection murmur. Abdomen: normal.

Labs in urgent care today: CBC: WBC of 20.8/cu mm, with 88% neutrophils, 2% bands, and 7% monocytes. Hemoglobin of 10.7 g/dL, hematocrit of 31.3%, platelet count of 715,000 g/dL, urinalysis normal, CRP 2.0. Chest radiograph shows bronchial thickening, unchanged from prior radiograph.

Assessment: Acute bronchiolitis. Patient will be admitted and put on bronchiolitis pathway, providing aggressive suctioning and supplemental oxygen as needed. Due to strong family history of asthma and exposure to tobacco smoke, we will monitor the patient closely.

ICD-10-CM code(s):

J21.9 Acute bronchiolitis, unspecified

Z77.22 Contact with and (suspected) exposure to environmental tobacco smoke (acute) (chronic)

Z82.5 Family history of asthma and other chronic lower respiratory diseases

Rationale: Since the child is diagnosed with acute bronchiolitis, the presence of coughing, difficulty breathing, and posttussive emesis

are not coded separately. The family history of asthma and the exposure to smoke are both important to code as they relate to the patient's respiratory issue. You are instructed, when applicable, to use additional codes to identify exposure to tobacco. This exposure is identified in codes representing environmental tobacco smoke, history of tobacco use, occupational exposure to environmental tobacco smoke, tobacco dependence, and tobacco use.

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This month in *CHEST*: Editor's picks

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

imultaneous Assessment of Hepatocyte Growth Factor and Vascular Endothelial Growth Factor in Epithe-

lial Lining Fluid From Patients With COPD. By Dr. H. Kanazawa et al. Laterality Defects Other Than Situs Inversus Totalis in Primary Ciliary **Dyskinesia: Insights** Into Situs Ambiguus and Heterotaxy. By Dr. A. J. Shapiro et al. Long-term Outcomes Following Development of New-Onset **Atrial Fibrillation During Sepsis.** By Dr. A. J. Walkey et al. **Detection of Fibrop**roliferation by Chest HRCT Scan in Resolving ARDS. By Dr. E. L. Burnham et al.

GIANTS IN CHEST MEDICINE **Richard W. Light, MD.** By Dr. J. H. Newman.

MEDICAL ETHICS **Physician Strikes.** By Dr. S. L. Thompson and J. W. Salmon.



CHEST Clinical Trials Registry is a path to more participation

re you a clinical trials investigator with unused capacity?

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Shanghai ahead: Announcing CHEST World Congress 2016

CHEST World Congress 2016 will be held in Shanghai, China, in April 2016. Clinicians spe-

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World Congress

2016

cializing in pulmonary, critical care, and sleep medicine from around the world

are expected to participate in the event, offered with support of the Chinese Thoracic Society.

Delegates who attend CHEST World

Congress 2016 in Shanghai will participate in a variety of educational

CHINA Shanghai • April 2016 ar

experiences ranging from hands-on simulation training and keynote addresses to

presentations by leading health-care experts and reports on the latest research in chest medicine.

More details coming soon!

Guidelines Methodology March 12-13

Innovation, Simulation, and Training Center Glenview, Illinois

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Guideline developers at novice or intermediate levels who want to improve their skills and knowledge of guideline development techniques and evidence review methodologies are encouraged to attend. Guidelines implementers, clinical decision tool designers, electronic health record programmers, performance measure developers, medical educators, and health policy makers are also encouraged to attend.

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medicine are encouraged to

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Bronson Healthcare Midwest in Kalamazoo, Michigan, is also seeking a Board Certified Pulmonologist to provide locums work a week or weekend per month for their established pulmonary group. The group provides inpatient consults and maintains an outpatient pulmonary practice, which is located on the campus of Bronson Methodist Hospital. Evening coverage is provided by the Bronson Adult Critical Care service. This would be an employed contracted position covering travel, meals and malpractice insurance.

Bronson Healthcare Midwest is a subsidiary of Bronson Healthcare Group in Kalamazoo, Michigan. The practice operates within Bronson Methodist Hospital which is an award winning, tertiary healthcare system serving 10 counties in southwest Michigan. With a workforce of more than 7,000, Bronson is one of the area's largest employers. We offer a full range of services from primary care to advanced critical care and have multiple service locations in Kalamazoo, Calhoun and Van Buren counties. Kalamazoo, located midway between Detroit and Chicago, is a diverse university town with highly rated public schools and affordable real estate. Offering art, symphony, theater, museums and year round festivals, there are many activities for the whole family including numerous parks, lakes, fine dining and Lake Michigan is less than an hour's drive away.

> For more information about Bronson or Kalamazoo visit www.bronsonhealth.com or www.kalamazoomi.com

Interested candidates my contact Cadace Lee at 269-341-8631 or leeca@bronsonhg.org

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Cambridge Health Alliance is a teaching affiliate of Harvard Medical School (HMS) and offers excellent opportunities for research and teaching. This position will have a faculty appointment to Beth Israel Medical Center and HMS commensurate with academic rank. At CHA we strongly encourage women and minorities to apply.

Please forward CV's to Laura Schofield, Senior Director of Physician Recruitment, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge MA 02139. Telephone (617) 665-3553, Fax (617) 665-3553 or via e-mail: Lschofield@challiance.org. EOE. www.challiance.org

South Florida Critical Care Medicine - <u>Nocturnist</u> An MHS representative will be attending the CHEST2014 Conference, visit us at booth#740

About the Opportunity:

Memorial Healthcare System's Intensivist program is expanding. The program is currently comprised of 21 full time intensivists, providing 24/7 ICU coverage at multiple locations within The Memorial Healthcare System. In addition to critical care, many of our intensivists hold multiple Board Certifications including infectious diseases, pulmonology, surgery and neuro-critical care. This is a full-time employed position with competitive benefits and compensation package, "sovereign immunity", paid CME, state of the art equipment (including EPIC EMS, digital Olympus bronchoscopes, intubation scopes, Glidescopes, Sonosite Ultrasounds etc)

Qualifications & Responsibilities: The program is seeking four (4) dedicated critical-care nocturnists to join the existing team. The nocturnists will integrate into the existing operational structure as the program expands to cover additional critical care units. Critical care coverage is provided in 12 hour in-house shifts, 7pm to7am - averaging approximately 15 shifts per month. The successful candidates will have excellent clinical skills, a broad knowledge base in critical care and be dedicated to providing high quality, evidence based care. Candidates must be BC/BE.

About Memorial Healthcare System:

Memorial Healthcare System is a 1,900-bed healthcare system located in South Florida and is highly regarded for its exceptional patient- and family-centered care. Memorial's patient, physician and employee satisfaction rates are among the most admired in the country, and the system is recognized as a national leader in quality healthcare.

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To inquire about this opportunity, visit www.memorialphysician.com







The how and where of telemedicine

Sleep Strategies from page 1

fashion to be a worthwhile endeavor within our ever-evolving field. Below, I discuss some practical considerations for current and future sleep telemedicine providers.

The backdrop

Telemedicine is defined as "the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status" (www.americantelemed.org). This definition is intentionally broad, allowing a wide range of telecommunication modalities to fall under its umbrella. We can counsel patients over the telephone, review their sleep testing results via secure

computer networks, and assess their CPAP data remotely.

Technology now allows us to examine patients from across the country. Clinical video telehealth (CVT) allows real-time video and audio communication between patients and their providers. This patient care technique is already used in other medical specialties, with one meta-analysis show-



DR. FIELDS

ing CVT to be less costly and at least as effective as in-person care (Wade et al. *BMC Health Services Research*. 2010;10[10]:233). While CVT for OSA has not been well-studied, one small trial showed equiv-

> alent patient satisfaction and CPAP adherence between in-person and CVT study arms (Parikh et al. *Telemed J E Health*. 2011;17[8]:609). Our challenge – and one that faces any potential telemedicine provider – is translating technologic capability into effective, feasible clinical care.

The resources

The technology needed for sleep telemedicine is readily available with more companies producing related products

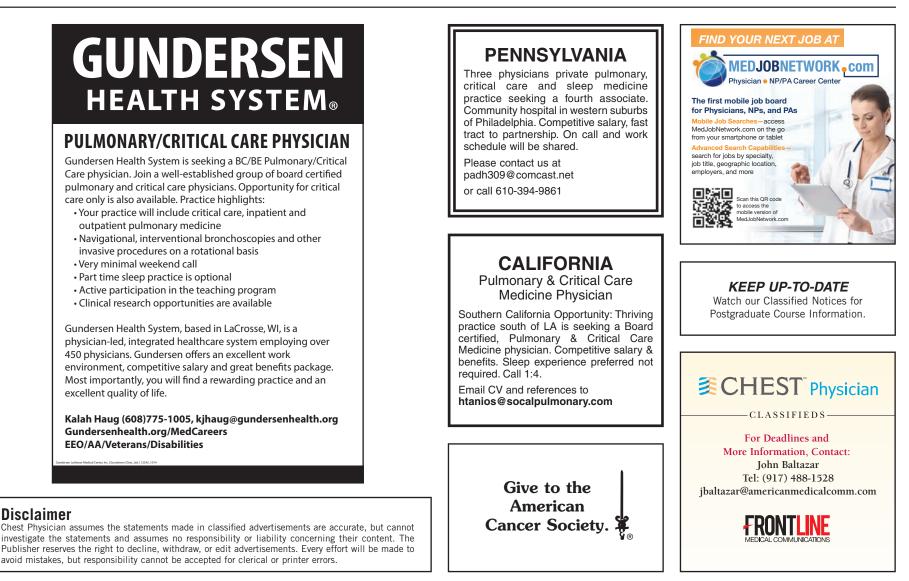
each passing year. Multiple manufacturers produce CVT consoles with a mounted high-definition camera for patient ("originating site") interviews, mobile cameras for detailed examination (eg, modified Mallampati score assessment), and electronic stethoscopes, with other new accessories constantly being added. Software links a distant-site provider's webcam and computer monitor to the originating site; I have found these interviews to be every bit as effective as in-person encounters. My center's program also employs an originating-site telemedicine technician who obtains vital signs, assists the distant-site provider with a modified physical examination, and troubleshoots any technological issues. Dovetailing nicely with these CVT encounters is remote CPAP adherence and effectiveness monitoring via online "clouds" (eg, Respironics EncoreAnywhereTM and Resmed AirViewTM). These store-and-forward platforms allow data transmission from CPAP machines to the Internet via modem or Bluetooth technology. Results can be shared with the patient during a CVT follow-up encounter.

Though these technologies for performing sleep telemedicine exist, do we have the economic means to implement them? Telemedicine carries a significant start-up price tag with ongoing maintenance-of-service costs. Major expenses include a telemedicine "cart" or console at the originating site (up to \$20,000), fees for space at that site, software to stream data to the provider, and compensation for the telemedicine professional at the originating site (eg, technician or nurse). Lost in-person visit revenue during telemedicine encounters should also be considered, particularly if compensation for these services is insufficient. *Continued on following page*

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PROFESSIONAL OPPORTUNITIES



Continued from previous page

Adequate reimbursement is essential to any telemedicine program's viability. Private insurance coverage rules vary greatly by the originating site's state. As of 2014, only 20 states require insurers to pay for telemedicine visits at parity with in-person visits; each state's status is available online at www.americantelemed.org. State-to-state Medicaid reimbursement also varies significantly, and the National Conference of State Legislatures provides a useful summary of coverage (www.ncsl.org/research/ health/state-coverage-for-telehealth-services.aspx). Currently, Medicare only reimburses real-time, CVT encounters when the originating facility is located in a health professional shortage area (HPSA) - defined as having a primary care to patient ratio of at most 1:3,500 - or in a county outside of a metropolitan statistical area as defined by the US Office of Management and Budget. These criteria, in addition to Medicare's excluding home-based telemedicine, can significantly limit the number of patients eligible for telemedical care. You can learn if a particular originating site is eligible for Medicare telehealth coverage through the US Department of Health and Human Services' website, available at datawarehouse.hrsa.gov/telehealthAdvisor/telehealthEligibility.aspx.

EDITOR'S NOTE

his month in Sleep Strategies, Dr. Fields discusses what may be one of the most important technological advances in the man-

agement of sleep apnea in quite some time. Patients often ask me about new advances in CPAP machines or interfaces that will make their therapy easier to use; the reality is that only a small minority of patients will benefit meaningfully from the new devices, and the recently-devel-

oped CPAP masks are not reliably better than the ones we have been using for years. Telemedicine, on the other hand, has the possibility of being a game-changer, allowing us to diagnose and monitor patients with sleep apnea who had previously been inaccessible due to distance or immobility. Combined with the availability of home sleep testing and adherence monitoring databases, we may soon enter an era in which sleep providers can

The clinical drivers

Is the financial investment and time commitment required to start a sleep telemedicine program balanced by a sufficient benefit to our patients? Available data suggest a robust "yes." New analyses from the Wisconsin Sleep Cohort show OSA to be a burgeoning public health challenge. The prevalence of moderate-to-severe OSA is now 3% among women and 10% among men between 30 and 49 years old. In those between 50 and 70, the prevalence is markedly higher, at 9% of women and 17% of men (Peppard et al. Am J Epidemiol. 2013;177[9]:1006). Most of these individuals remain undiagnosed, exposing them to the well-described sequelae of untreated sleep-disordered breathing (Kapur et al. Sleep Breath. 2002;6[2]:49).

One factor contributing to OSA underdiagnosis is a lack of access to care; more than 59 million Americans live in medical HPSAs with limited primary care resources. Specialists are generally even harder to access in these areas. While the sleep specialist shortage is difficult to quantify, an Association of American Medical Colleges (AAMC) report found patient-to-pulmonologist and patient-to-neurologist ratios of 24,673:1 and 23,928:1, respectively (AAMC. Physician Specialty Data Book. 2012). Since many of these providers do not practice sleep medicine (and despite some other specialists who do), a

large supply-and-demand disparity likely exists. Fortunately, telemedicine is already being used to narrow that gap. Outlying facilities have developed telemedicine agreements with academic medical centers, allowing sleep specialists direct consultation with medically underserved patients (Spaulding et al. J Telemed Telecare. 2011;17[7]:346).

Similar challenges exist within the VA system. In my own VA Southeast Network, approximately 48% of veterans live in rural areas. These individuals account for almost 1.5 million outpatient visits annually, contributing to significant wait times and driving up VA travel reimbursement costs. While we have just begun instituting CVT in some specialty clinics (including sleep), other VA Medical Centers have already seen telemedicine's benefits come to

fruition. The Richard L. Roudebush VA Medical Center in Indianapolis reports a \$662,264 reduction in travel reimbursements in the first 3 years of its multispecialty CVT program, with an average of 90 miles saved per veteran and overall patient satisfaction at 96% (Wennergren et al. Int J Clin Med. 2014;5:711).

The opportunities

As previously noted, Medicare's restrictive policies have stifled efforts to expand telemedicine, but a new opportunity may soon lower those hurdles. The proposed Medicare Telehealth Parity Act of 2014 expands coverage to millions of Americans. Over the next 4 years, this legislation would remove geographic coverage restrictions, cover care originating from a patient's home, and add coverage for store-and-forward technologies (eg, PAP download reviews). This could mean the difference between telemedicine viability and insolvency within the private sector. As of this writing, final approval looks like it will wait until after the 2014 midterm elections.

Another opportunity for telemedicine expansion exists secondary to changes in state medical licensing rules. Telemedicine practitioners caring for out-of-state patients often need a medical license in each of those patients' states. These licens-

A sleep telemedicine cart features a high-definition camera, video monitors, and a telestethoscope, which allow for real-time interaction with patients.

ing requirements particularly impact sleep medicine; each provider within a group practice who shares sleep study interpretation responsibilities would need additional licensing to serve any out-of-state patients. Fortunately, the Federation of State Medical Boards is finalizing its Interstate Medical Licensure Compact. Scheduled to be released in 2015, the Compact would be a legally binding agreement among states, allowing physicians to have a rapid, streamlined mechanism for interstate licensing approval. While individual state governments would need to enact the Compact, it was recently touted as "herald[ing] a major reform in medical licensing" (Steinbrook et al. JAMA. 2014;312[7]:695).

Concluding remarks

Sleep telemedicine is in its infancy, and significant growing pains remain. There is little precedent to chart its course, and even less research to inform its implementation. Nevertheless, existing resources, clinical drivers, and growth opportunities only heighten my conviction that it will serve an important role in our growing field.

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treat a greater number of patients more rapidly and reliably than is currently feasible.

Adoption of telemedicine by

sleep apnea practices will not be without its challenges. In an era of shrinking remuneration for sleep specialists, the start-up costs are going to be a major impediment to implementation, and insurers will need to commit to compensating us for time spent on clinical care, even if we

are unable to physically touch the patients we are managing. However, given the growing imbalance between sleep apnea prevalence and the availability of qualified sleep-medicine providers, telemedicine may be just the tool we need to keep the ramifications of untreated sleep apnea at a greater distance from our patients.

Dr. David A. Schulman, FCCP Section Editor





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