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VIVIAN E. LEE/ELSEVIER GLOBAL MEDICAL NEWS

Baltimore City Health Commissioner Dr. Joshua Sharfstein testified against use of over-the-counter cough and cold products in children.

FDA Plans Guidance on OTC Cold Meds for Kids

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

SILVER SPRING, MD. — The Food and Drug Administration is expected to issue interim recommendations to the public about the use of over-the-counter cough and cold products in children, in response to the advisory panel recommendation that these products not be used in children under age 6.

On Oct. 19, at the end of a 2-day meeting on the safety and efficacy of OTC cough and cold products in children, the FDA's Nonprescription Drugs and Pediatric advisory committees agreed that there was no evidence from the available scientific studies that these products were effective in children under

age 12, and they expressed concerns about extrapolating evidence about efficacy and safety obtained in adults to children, and from older children to younger children.

The panels voted 13-9 that these products should not be used in children aged 2-5. But they voted 15-7 against recommending that they not be used in children aged 6-11.

The committees voted 21-1 that these products should not be used for children under age 2. OTC cough and cold products are not approved by the FDA for this age group, and their labels include the statement advising consumers to ask their doctor before using these products in this age

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Study: Invasive MRSA Is a 'Major' Health Problem

Incidence at 31.8 per 100,000 people.

BY KATE JOHNSON
Elsevier Global Medical News

The prevalence of methicillin-resistant *Staphylococcus aureus* infections in the United States may be higher than previously thought and represents a major public health problem, according to a nationwide estimate of the burden of the disease, reported R. Monina Kleven, D.D.S., of the Centers for Disease Control and Prevention, and colleagues.

The authors estimated the standardized incidence of invasive MRSA in the year 2005 to be 31.8 per 100,000 persons, with the highest rates in people aged 65 years and older (127.7 per 100,000), in blacks (66.5 per 100,000), and in males (37.5 per 100,000). The majority of disease was related to health care but occurred outside the health care setting, they noted (*JAMA* 2007;298:1763-71).

The study used population-based, active case-finding to come up with national estimates

of invasive MRSA incidence and mortality rates. As part of the Active Bacterial Core surveillance system, a component of the Emerging Infections Programs Network of the CDC, nine sites conducted surveillance for invasive MRSA. The total population under surveillance was estimated to be 16.5 million, or approximately 5.6% of the U.S. population. Results were then used to estimate the nationwide incidence.

Medical records were used to document health care risk factors for MRSA, and cases were classified as either health care-associated or community-associated.

A standardized incidence of 31.8 per 100,000 was estimated from a total of 8,987 observed cases of invasive MRSA. The study found that 14% of infections were community associated and 85% were health care associated, with 58% of the latter being community onset and 27% being hospital onset.

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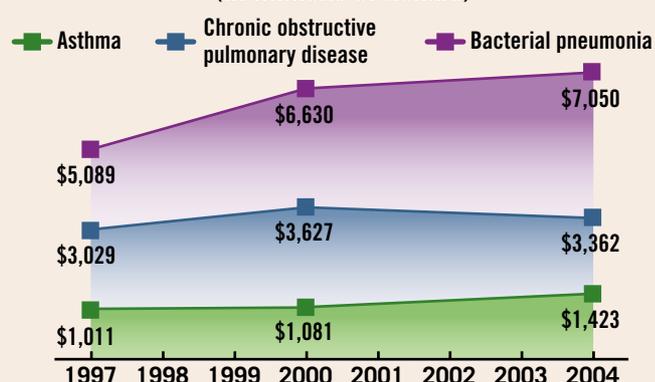
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VITAL SIGNS

Costs of Preventable Hospitalizations For Respiratory Conditions (in millions of dollars)



Note: Amounts adjusted for inflation to 2004 dollars using the overall Consumer Price Index.

Source: Healthcare Cost and Utilization Project

Gene Predicted Lung Cancer Outcomes

BY ERIK GOLDMAN
Elsevier Global Medical News

BARCELONA — Overexpression of BRCA1, one of the genes associated with aggressive breast cancer, also predicts cisplatin resistance, faster recurrence, and reduced survival in people with non-small cell lung cancers, Dr. Rafael Rosell reported at the 14th European Cancer Conference.

Dr. Rosell and colleagues at the Catalan Institute of Oncology have been studying gene expression signatures that predict the behavior and treatment responsiveness of lung tumors. They've identified nine genes, all involved in the process of DNA repair, that may have potential predictive value. By far the biggest red flag is BRCA1. The investigators assessed

expression of these nine genes in tumor tissue obtained from 126 people with stage IA-IIIa squamous cell carcinoma or adenocarcinoma. Overall, 42% of patients had stage IB tumors, and 26% had stage II lesions. BRCA1 was the only gene of the nine to show independent prognostic value as far as clinical outcomes.

Patients in the uppermost quartile of BRCA1 expression showed much greater resistance

to cisplatin-based treatment regimens, and were twice as likely to die within 3 years, compared with those in the lowest quartile. Median time to recurrence was 22 months among the high BRCA1 expressors, and median survival was 29 months. Among those in the lowest quartile, the majority was still alive and disease free after 3 years.

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Antibiotics' Impact Mixed in Respiratory Infections

BY JONATHAN GARDNER
Elsevier Global Medical News

Prescribing antibiotics for respiratory tract infections rarely averts complications, although they may be effective in preventing pneumonia among older patients with chest infections, according to an analysis of British patient records.

The analysis of more than 3 million records from 162 British practices over 10 years found that the risk of mastoiditis after otitis media, peritonsillar abscess after sore throat, and pneumonia after upper respiratory infection was too low to justify antibiotics (BMJ 2007 Oct. 19 [Epub doi:10.1136/bmj.39345.405243.BE]).

The researchers from University College London and the British Health Protection Agency calculated that more than 4,000 otitis media, sore throat, or respiratory tract infections would need to be treated to avert a single complication.

However, they found a greater effect on treating chest infections. Among patients

maybe for acute otitis media," they wrote. "For lower respiratory tract infections in particular, clinicians cannot be confident about identifying who will benefit from antibiotics and who will not."

The researchers examined 3.36 million records of respiratory infections in the UK General Practice Research Database between July 1, 1991, and June 30, 2001. The records were used to identify patients who developed complications in the month following their diagnoses, excluding those recorded on the day of diagnosis, and to

calculate the risks of complication based on prescription for antibiotics.

The researchers acknowledged that their methods may have influenced the findings. Patients with severe disease, and thus a greater risk of complications, may have been more likely to be prescribed antibiotics, which may have resulted in an underestimate of the protective effect of antibiotics, the researchers wrote.

In addition, patients with pneumonia are more likely to be treated in secondary care, so they might not have been recorded as

part of the general practice database, which also could have led to an underestimation of the risk of complications.

However, the researchers added, cases of bronchitis may have been misclassified as pneumonia by physicians wishing to prescribe antibiotics, which may have led to an overestimation of the risk of pneumonia after chest infection and an overestimation of the protective effect of antibiotics.

Dr. Livermore and Dr. Johnson have contractual agreements with pharmaceutical companies that produce antibiotics. ■

TREATING 39 CASES OF CHEST INFECTION WITH ANTIBIOTICS IN PEOPLE AGED 65 YEARS AND OLDER WOULD PREVENT ONE CASE OF PNEUMONIA.

aged 65 years and older, the researchers found that treating 39 cases of chest infection with antibiotics would prevent one case of pneumonia. Even younger patients experienced limited benefits: For age groups between 0 and 64, the number of cases treated with antibiotics that would prevent pneumonia ranged between 96 and 119. The authors noted that only a relatively low number of antibiotic courses was required for the preventive effect.

"There are legitimate concerns about the overuse of antibiotics in primary care and the development of resistance," wrote the researchers, led by Irene Petersen, statistician at University College London's Centre for Infectious Disease Epidemiology. "General practitioners should not base their prescribing for sore throat, otitis media, or upper respiratory tract infections on a fear of serious complications. In contrast, antibiotics substantially reduce the risk of a diagnosis of pneumonia after chest infection."

With lower respiratory tract infections, the researchers noted, it is difficult to distinguish between acute bronchitis, for which antibiotics are not recommended, and early pneumonia, for which antibiotics are recommended, without chest radiography, which is unavailable at many practices.

In an accompanying commentary, Dr. Samuel Coenen and Dr. Herman Goossens of the University of Antwerp wrote that while the research supports the recommendations against overprescribing of antibiotics, it does not help physicians make tough calls in the examination room.

"The available evidence does not provide clinicians with the guidance they need to prescribe antibiotics effectively for common infections in primary care, except

THE POWER TO HELP THEM QUIT

DUAL ACTION FOR SMOKING CESSATION

- CHANTIX™ (varenicline) has agonist and antagonist effects at $\alpha_4\beta_2$ nicotinic acetylcholine receptors



CHANTIX is indicated as an aid to smoking cessation treatment in adults.

Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied.

Zyban is a registered trademark of Glaxo Group Limited.

References: 1. Food and Drug Administration, Center for Drug Evaluation and Research. Approval package for: application number NDA 21-928: statistical review(s). Food and Drug Administration Web site. Available at: http://www.fda.gov/cder/foi/nda/2006/021928_s000_Chantix_StatR.pdf. Accessed August 25, 2006. 2. Data on file. Pfizer Inc. Post hoc analysis of data from final study reports. 3. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55. 4. Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63. 5. CHANTIX [package insert]. New York, NY: Pfizer Inc; May 2007.

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Please see brief summary of Prescribing Information on last page of this advertisement.

Gene May Affect Cisplatin Response

Lung Cancer • from page 1

The data suggest that only 30% of the high expressors would still be alive at 40 months after surgery, while 70% of the low expressors would survive. By 60 months, the probability of survival drops to about 20% for those with high-BRCA1 primary tumors, but remains around 60% for the low expressors. Overall, having a high-BRCA1-expressing tumor doubled the hazard ratio for recurrence and mortality, compared with having a low-BRCA1-expressing tumor.

“BRCA1 was the only one of the genes that showed significant correlations with clinical outcome and the only independent prognostic variable other than tumor stage of IIIA or higher,” Dr. Rosell said at the conference, which was sponsored by the Federation of European Cancer Societies.

He and his colleagues obtained very consistent findings in a validation cohort of 58 patients. They will publish a retrospective analysis before the end of this year, and they are actively developing a prospective

trial to validate and quantify the predictive value of BRCA1 expression.

BRCA1 plays a central role in repair of DNA damage. Several earlier studies have shown that low levels of BRCA1 expression correlate well with cisplatin sensitivity, while increased BRCA1 expression is associated with treatment resistance.

“Since cisplatin is the gold standard drug for adjuvant chemotherapy in high-risk resected lung cancers, we think these findings could have significant therapeutic impact,” he said. “Perhaps those patients with high-BRCA1-expressing tumors should just bypass cisplatin altogether, and go directly to taxane-based therapies.”

Commenting on the presentation, Dr. Alexander Eggermont, president of the newly formed ECCO organization, said, “If this will be validated in future studies, it will really change the landscape of diagnostic testing and treatment decision making.”

Dr. Rosell expects a long debate before practices change. Because cisplatin has been the standard of care for non-small cell lung cancer for so long, he explained, and because nearly all of the clinical trials for these cancers are cisplatin-based, there will likely be a fair amount of resistance to anything that challenges the preeminence of the drug or suggests that some patients would be better off without it. ■

QUIT RATES SUPERIOR TO ZYBAN® AT 12 WEEKS IN 2 HEAD-TO-HEAD CLINICAL TRIALS (P=.0001)^{1,2*}

44% of subjects who received CHANTIX 1 mg bid quit smoking by the end of 12 weeks vs:

- Approximately 30% of subjects who received Zyban 150 mg bid
- Approximately 17.5% of subjects who received placebo

WELL-STUDIED TOLERABILITY AND SAFETY PROFILE

- The most common adverse reactions included nausea, sleep disturbance, constipation, flatulence, and vomiting. Nausea occurred in 30% of subjects while 3% discontinued due to nausea

CONVENIENT PAK DOSING

- PAKs are designed to simplify prescribing and to help improve patient adherence

GET SUPPORT PLAN

- A personalized behavioral support program designed to address critical behavioral components of smoking cessation, such as relapse

Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.

Dosage adjustment with CHANTIX is recommended in patients with severe renal impairment or in patients undergoing hemodialysis.

Smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, such as theophylline, warfarin, and insulin. Dosage adjustment for these drugs may be necessary.

CHANTIX[™]
(varenicline) TABLETS

TURN MORE SMOKERS INTO QUITTERS

*Results from 2 identically designed, 52-week (12 weeks pharmacotherapy, 40 weeks nonpharmacotherapy follow-up), randomized, double-blind, parallel-group, multicenter clinical trials (study 4: N=1022; study 5: N=1023) in which CHANTIX 1 mg bid was compared with Zyban 150 mg bid and placebo for efficacy and safety in smoking cessation. For trial inclusion, subjects must have smoked at least 10 cigarettes per day over the past year, with no period of abstinence greater than 3 months, and must have been bupropion naive. The primary efficacy end point in both trials was the carbon monoxide (CO)-confirmed 4-week continuous abstinence rate for weeks 9 through 12, defined as the percentage of subjects who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled CO measurement of 10 ppm or less at each clinic visit. (Studies 4 and 5 from the CHANTIX package insert.)^{1,2,5}

Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.³

Placenta No Barrier to H5N1 Avian Influenza

BY JONATHAN GARDNER
Elsevier Global Medical News

In humans, the highly pathogenic H5N1 avian influenza virus can spread beyond the lungs and also can cross the placenta to the fetus, according to research published in the Lancet.

Chinese researchers examined the post-mortem tissues of two adults, a 35-year-old man from Jiangxi province and a 24-year-old woman from Anhui province who was 4 months' pregnant. Both individuals were

confirmed as infected with H5N1 by the Chinese Centre for Disease Control and Prevention (Lancet 2007;370:1137-45).

Examination of tissues from the respiratory, digestive, and central nervous systems, and from other organs found viral genetic material and antigens to the virus. In the respiratory system, the researchers found signs that H5N1 had affected, among other tissues, the alveoli, in contrast to human influenza, which mainly targets the upper respiratory tract.

In the pregnant woman, the researchers

found infected cells in the placenta and, in the fetus, they found viral sequences in the lungs, circulating mononuclear cells, and the liver.

The woman had been admitted after 6 days of fever, cough, and shortness of breath. She had handled ill birds 2 weeks before admission and died 2.5 days after, despite treatment with antibiotics and corticosteroids. No antivirals were given, the investigators noted.

The man died 27 days after developing fever and productive cough. Admitted to

the hospital with a 6-day history of symptoms, he was first administered corticosteroids, followed by an antiviral, and then antifungal treatments.

The researchers said their findings help shed light on how H5N1 infections progress, which will be important for public health officials to watch because that strain of virus is feared as the most likely to result in a pandemic.

"Little is known about the specific effects in organs and cells targeted by the virus," wrote the researchers, led by Dr. Jiang Gu of Peking University in Beijing. "The infection initially seemed to be restricted to the lungs, but later reports have suggested that influenza A H5N1 could disseminate beyond the lungs," they said.

"These newly obtained data are important in the clinical, pathological, and epidemiological investigation of human

IN A PREGNANT WOMAN, RESEARCHERS FOUND INFECTED CELLS IN THE PLACENTA AND VIRAL SEQUENCES IN THE FETUS'S LUNGS AND LIVER.

H5N1 infection and have implications for public-health and health care providers," they added.

In all, the researchers found viral genetic material and antigens in epithelial cells of the lungs and trachea, T cells of the lymph nodes, neurons of the brain, and Hofbauer cells and cytotrophoblasts of the placenta. They found viral genomic sequences but no antigens in the intestinal mucosa.

The route of infection for the central nervous system could be through the blood-brain barrier or through respiratory system nerves after replicating in tissues there, the researchers wrote.

For the intestines, the virus could be blood borne but could occur through the ingestion of respiratory secretions, they added.

How the vertical infection of the fetus would affect the fetus is unclear. Human influenza strains infecting a pregnant female have not been shown to affect the fetus, but since H5N1 also has effects on humans not seen in human strains, such as viremia, "the likelihood of virus reaching the uterus and placenta is probably higher in avian influenza than in human influenza," they wrote.

In an accompanying commentary, Dr. Wai Fu Ng of Princess Margaret Hospital in Hong Kong and Professor Ka Fai To of Chinese University of Hong Kong raise questions about the effects of the vertical infection route.

"The absence of pathological changes in the immunologically incompetent fetus is taken as evidence that viral replication itself is not pathogenic," they wrote. "Speculation about the fate of the fetus if the mother survived the infection is interesting.

"With the development of antibodies in the mother and their transplacental crossing into the fetus, pathological lesions in the fetus may result," they said.

CHANTIX™
(varenicline) TABLETS

INDICATIONS AND USAGE
CHANTIX is indicated as an aid to smoking cessation treatment.

PRECAUTIONS

General Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Effect of smoking cessation: Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

Drug Interactions Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis. Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of fibroma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis. Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of fertility. There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Pregnancy Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Nonreproductive effects** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **DOSE AND ADMINISTRATION, Special Populations, Patients with impaired renal function**). No dosage adjustment is recommended for elderly patients (see **DOSE AND ADMINISTRATION, Special Populations**).

Information for Patients:

- Patients should be instructed to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date.
- Patients should be advised that CHANTIX should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.
- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should be informed that nausea and insomnia are side effects of CHANTIX and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify their prescribing physician so that a dose reduction can be considered.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with CHANTIX.
- Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

ADVERSE REACTIONS

During the premarketing development of CHANTIX, over 4500 individuals were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for CHANTIX compared to 10% for placebo in studies of three months' duration. In this group, the discontinuation rates for the most common adverse events in CHANTIX treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.3% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo). Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting. Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

The most common adverse event associated with CHANTIX treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dose titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Table 3 shows the adverse events for CHANTIX and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as "insomnia", "middle insomnia", "middle insomnia", "Early morning awakening" were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4



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(Table 3 continued)

PSYCHIATRIC DISORDERS			
Sleep Disorders/Disturbances			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIRATORY/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia		2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3, though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS.** *Infrequent:* Anemia, Lymphadenopathy. *Rare:* Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS.** *Infrequent:* Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia. *Rare:* Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome. **EAR AND LABYRINTH DISORDERS.** *Infrequent:* Tinnitus, Vertigo. *Rare:* Deafness, Meniere's disease. **ENDOCRINE SYSTEMS.** *Infrequent:* Thyroid gland disorders. **EYE DISORDERS.** *Infrequent:* Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. *Rare:* Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS.** *Frequent:* Diarrhea, Gingivitis. *Infrequent:* Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. *Rare:* Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS.** *Frequent:* Chest pain, Influenza like illness, Edema, Thirst. *Infrequent:* Chest discomfort, Chills, Pyrexia. **HEPATOBIILIARY DISORDERS.** *Infrequent:* Gall bladder disorder. **IMMUNE SYSTEM DISORDERS.** *Infrequent:* Hypersensitivity. *Rare:* Drug hypersensitivity. **INVESTIGATIONS.** *Frequent:* Liver function test abnormal, Weight increased. *Infrequent:* Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS.** *Infrequent:* Diabetes mellitus, Hyperlipidemia, Hypokalemia. *Rare:* Hyperkalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS.** *Frequent:* Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. *Infrequent:* Arthritis, Osteoporosis. *Rare:* Myositis. **NERVOUS SYSTEM DISORDERS.** *Frequent:* Disturbance in attention, Dizziness, Sensory disturbance. *Infrequent:* Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. *Rare:* Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS.** *Frequent:* Anxiety, Depression, Emotional disorder, Irritability, Restlessness. *Infrequent:* Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. *Rare:* Bradyphrenia, Euphoric mood, Hallucinations, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS.** *Frequent:* Polyuria. *Infrequent:* Nephrothiasis, Nocturia, Urine abnormality, Urinary syndrome. *Rare:* Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAST DISORDERS.** *Frequent:* Menstrual disorder. *Infrequent:* Erectile dysfunction. *Rare:* Sexual dysfunction. **RESPIRATORY AND MEDIASTINAL DISORDERS.** *Frequent:* Epistaxis, Respiratory disorders. *Infrequent:* Asthma. *Rare:* Pleurisy, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS.** *Frequent:* Hyperhidrosis. *Infrequent:* Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria. *Rare:* Photosensitivity reaction. **VASCULAR DISORDERS.** *Frequent:* Hot flush, Hypertension. *Infrequent:* Hypotension, Peripheral ischemia, Thrombosis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Varenicline is not a controlled substance. **Humans:** Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. **Animals:** Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

OVERDOSEAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations), however, there is no experience in dialysis following overdose.

DOSE AND ADMINISTRATION

Usual Dosage for Adults Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1-3:	0.5 mg once daily
Days 4-7:	0.5 mg twice daily
Days 8-End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Special Populations

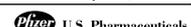
Patients with impaired renal function No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal Impairment).

Dosing in elderly patients and patients with impaired hepatic function No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See PRECAUTIONS, Geriatric Use).

Use in children Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Rx only

May 2007, Version 2.0



Cardiac Troponin I May Signal Pulmonary Embolism Risk

BY BRUCE K. DIXON
Elsevier Global Medical News

CHICAGO — The measurement of cardiac troponin I should be routinely performed in all emergency department patients in whom pulmonary embolism is suspected, according to a study led by Dr. Hamid Shokoohi.

A troponin (cTnI) level greater than 0.08 ng/mL should raise concern for central pulmonary vascular obstruction, especially in patients without overt clinical evidence of circulatory compromise, Dr. Shokoohi said at the annual meeting of the Society for Academic Emergency Medicine.

“Troponin has been shown to be of clinical benefit in prediction of in-hospital mortality and adverse outcome in pulmonary embolism,” said Dr. Shokoohi, senior resident in emergency medicine at George Washington University, Washington.

Right heart failure is the usual cause of death from pulmonary embolism (PE), and right ventricular (RV) dysfunction may be an important warning sign of a bad outcome. “Cardiac echo is most frequently utilized to evaluate RV strain, but 2D echo is not available 24 hours a day, 7 days a week in most institutions,” Dr.

Shokoohi explained. The proximal level of PE is associated with the severity of PE determined by clinical, biochemical, and radiologic markers, he added.

The retrospective cohort study began with 179 emergency department patients diagnosed with PE over a 2-year period. After exclusion of patients who had not been tested for elevated troponin (52), those for whom a CT scan was not available (14), and other reasons, the final study sample was 104 patients.

To rule out chronic PE, only patients with a prior onset of symptoms of less than 2 weeks were accepted. The mean duration of symptoms among 20 patients with elevated troponin was 29 hours, compared with 44 hours among 84 patients with normal troponin.

Women made up 80% of patients in the elevated troponin group of patients, and were a 53% majority among those with normal troponin. The mean ages of the cohorts were 53 years and 51 years, respectively.

Diagnosis of PE was confirmed by spiral CT and high-probability ventilation perfusion scans.

The primary outcome measure was main pulmonary artery involvement; the

secondary outcomes were ICU admissions, emergency department mortality, and the use of thrombolytic therapy.

The main pulmonary artery was involved in 70% of those patients with elevated troponin and only 14% of those with normal troponin. Lobar involvement was seen in 25% and 33% of each group respectively, Dr. Shokoohi reported.

“In determining the accuracy of cTnI to predict main pulmonary artery involvement, we had a sensitivity of 54%, a specificity of 92%, a negative predictive value of 86% and a positive predictive value of 75%,” he said.

Increased troponin level also was highly correlated with ICU admission of patients with PE. A total of four patients with elevated troponin received thrombolytic therapy, versus none in the normal troponin group. There was a single ED death among the 20 patients with elevated troponin.

Dr. Shokoohi described several limitations of this study, including its single-institution retrospective nature, the exclusion of 36% of eligible patients because of a lack of a cTnI measurement or CT images, and possible physician awareness of troponin results and its potential

effect on ICU admissions.

“But based on this study, if you have confirmed PE based on a CT scan and the patient has a negative troponin, he or she is less likely to have central pulmonary embolism,” Dr. Shokoohi said.

Coauthors of the study included Dr. Robert Shesser, Dr. Jeffrey Smith, Dr. Michael Hill, and Dr. Robert Hirsh. ■

Dr. Keith Wille, FCCP, comments:
Dr. Shokoohi's results are further supported by a recent study (*Circulation* 2007;116:427-33) examining the prognostic value of troponins in acute pulmonary embolism (PE). In their meta-analysis, Becattini et al. reviewed 20 studies (1,985 patients) and found that 19.7% of patients with elevated troponin levels died, compared with 3.7% of patients with normal troponin levels. Elevated troponin levels were associated with higher short-term mortality (OR 5.24, 95% CI 3.28-8.38), death due to PE (OR 9.44, 95% CI 4.14-21.5), and adverse outcome events (OR 7.03, 95% CI 2.42-20.4). While these findings are intriguing, it is still unclear whether biological markers such as troponin may lead to better risk stratification, treatment decisions, and clinical outcomes for all PE patients.

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MRSA's Toll 'Astounding'

Health Problem • from page 1

A total of 114 infections (1%) could not be classified. There were an estimated 18,650 deaths from invasive MRSA, giving a standardized mortality rate of 6.3 per 100,000.

The estimated incidence is “astounding,” Dr. Elizabeth A. Bancroft commented in an accompanying editorial (*JAMA* 2007;298:1803-4). “To put this number into context, the estimated rate of invasive MRSA is greater than the combined rate in 2005 for invasive pneumococcal disease (14.1 per 100,000), invasive group A strep-

tococcus (3.6 per 100,000), invasive meningococcal disease (0.35 per 100,000), and invasive *H[aemophilus] influenzae* (1.4 per 100,000),” said Dr. Bancroft, of the Los Angeles County Department of Public Health.

In addition, if the authors' projected mortality rate is accurate, “these deaths would exceed the total number of deaths attributable to human immunodeficiency virus/AIDS in the United States in 2005,” added Dr. Bancroft.

The authors noted that their estimated

incidence is higher than that of a recent CDC study (*Emerg. Infect. Dis.* 2005; 11:868-72). Compared with previously documented incidence rates (2001-2002) at two of the study sites, there was an increased incidence observed in Atlanta (from 19 to 33 per 100,000) and Baltimore (from 40 to 117 per 100,000). However, in the state of Connecticut, the 2005 incidence of 2.8 per 100,000 was relatively stable, compared with a 1998 incidence of 2.5 per 100,000, they wrote.

“Invasive MRSA disease is a major public health problem and is primarily related to health care but no longer confined to acute care,” the study's authors concluded. ■

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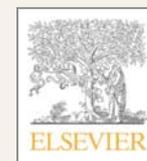
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Bosentan Slowed Progression of Class II PAH

BY MITCHEL L. ZOLER
Elsevier Global Medical News

VIENNA — Patients with functional class II pulmonary arterial hypertension had significantly slower disease progression when treated with bosentan in a study with 185 patients, a finding that may shift the time to diagnose and start treatment of this disease.

The results support starting treatment of pulmonary arterial hypertension (PAH) “as soon as possible after the diagnosis is made because the majority of patients with PAH are in functional class II or III; the majority of PAH patients need treatment [with bosentan] according to these data,” Dr. Nazzareno Galiè said at the annual congress of the European Society of Cardiology.

“In PAH it’s very important to prevent deterioration, and that’s what treatment

with bosentan does,” said Dr. Galiè. “The results show that PAH is a progressive disease, even in class II, highlighting the need for early diagnosis and treatment.”

The Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients (EARLY) study “is the only study to focus on class II patients,” and it included a strict definition of class II, said Dr. Galiè, professor of cardiology and head of the Pulmonary Hypertension Centre at the University of Bologna (Italy).

Based on these and other findings, applications have been filed with the Food and Drug Administration and similar agencies in other countries to expand bosentan treatment to patients with class II PAH. Bosentan (Tracleer) is already marketed for treating classes III and IV PAH by Actelion.

The new study was sponsored by Actelion, and Dr. Galiè is a speaker for and consultant to Actelion.

“The EARLY study results, and the results from [five] other studies that included class II PAH patients, support the benefit of treating patients with less-severe PAH. The added strength of the data from EARLY is that they demonstrated in a pure cohort of class II patients that early treatment may delay progression of the disease,” commented Dr. Lewis J. Rubin, FCCP, a coauthor of the study and professor of medicine and director of pulmonary and critical care medicine at the University of California, San Diego. Dr. Rubin is a consultant to Actelion.

The study enrolled patients aged 12 years and older, mean age 44, with PAH rated as functional class II by World Health Organization criteria.

The disease could have been idiopathic (as it was in about 60% of patients), or

caused by congenital heart disease (in about 17%), connective tissue disease (in about 18%), or HIV infection (in about 5%). The average duration of PAH was about 3 years.

Patients were randomized to treatment with either 62.5 mg bosentan b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 5 months, or placebo.

After 6 months of treatment, the change from baseline in pulmonary vascular resistance, one of two primary end

points, was increased by about 7% among 88 evaluable patients in the placebo group, and was decreased by about 16% in 80 patients in the bosentan group. The overall effect of bosentan treatment was to lower pulmonary vascular resistance by 23%, compared with placebo, a significant effect.

The second primary end point was change in exercise capacity, measured by distance walked in 6 minutes.

By this measure, bosentan was linked

to a significant, 19-m boost in distance walked, compared with placebo, Dr. Galiè reported.

Bosentan treatment also led to significant improvements in time to clinical worsening, and a decrease in the percentage of patients whose condition worsened. Symptomatic progression of PAH occurred in 10% of patients on placebo, compared with 1% of the patients treated with bosentan.

With bosentan, Dr. Galiè said, “there is

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Deep Venous Thrombosis and Pulmonary Embolism in Hospitalized Patients With Acute Respiratory Diseases Including COPD

The importance of appropriate evidence-based pharmacologic prophylaxis

James T. Good Jr, MD

Up to 2 million Americans suffer from deep venous thrombosis (DVT) annually,¹ and approximately 300,000 die from pulmonary embolism (PE),² most cases of which result from DVT.³ Complications from DVT kill more Americans than AIDS and breast cancer combined.¹ DVT/PE risk is increased in patients with comorbid conditions and various risk factors, including acute respiratory diseases.⁴

Eleven million US adults are affected by chronic obstructive pulmonary disease (COPD).⁵ Each year, as many as 3.5 million hospitalizations occur for the management of COPD.⁶

Hospitalized COPD Patients Are at Increased Risk for Developing DVT

Hospitalized patients with acute respiratory disease are at risk for DVT, which may lead to PE, the most common cause of preventable hospital death.⁷ In fact, up to 25% of hospitalized patients with respiratory disease may have DVT.⁸ Conversely, statistics from a registry of consecutive patients with acute PE indicate that 14% of these patients have COPD.⁹ At autopsy, one study found that up to 51% of COPD patients had comorbid PE.¹⁰ The common overlap of these conditions may be partly attributable to the fact that many risk factors for DVT are also often present in patients with COPD (Table 1).⁷

Table 1. Common DVT/PE Risk Factors Present in Patients With COPD

• Reduced mobility	• Smoking
• Polycythemia	• Previous DVT
• Infection	• Mechanical ventilation
• Heart failure	• Obesity

Evidence-based Guidelines Recommend Medical Prophylaxis

The 2004 ACCP Guidelines on the Prevention of Venous Thromboembolism recommend prophylaxis with either low-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for acutely ill medical patients admitted to the hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors.⁷

The guidelines state explicitly that waiting for symptomatic DVT or PE before taking action may have

fatal consequences.⁷ Nevertheless, national data indicate only 53.9% of medical patients with COPD receive anticoagulants.¹¹ Appropriate prophylaxis takes on an additional urgency in hospitalized patients with COPD because symptoms of acute respiratory disease may mask comorbid PE.¹²

COPD Exacerbation, PE, or Both? The Diagnostic Challenge

COPD exacerbation and PE have similar signs, symptoms, and radiographic findings (Table 2).^{12,13} And the usual diagnostic standbys for identification of PE may have reduced prognostic value in the patient with COPD; it has been noted that in this patient group, V/Q scans yield less information than in patients with no cardiopulmonary disease or cardiopulmonary disease exclusive of COPD.¹³

Table 2. Most Frequent Symptoms, Signs, and Radiographic Findings in Patients With COPD and Suspected Acute PE

• Dyspnea	• Wheezing
• Cough	• Atelectasis
• Pleuritic pain	• Effusion

LOVENOX® (enoxaparin sodium injection) Provided Effective Thromboprophylaxis

In the MEDENOX (Prophylaxis in Medical Patients with Enoxaparin) study, 1102 patients with acute medical illness were enrolled. A majority (53%) had chronic respiratory failure. In a double-blind comparison to placebo, 40 mg once daily LOVENOX® was associated with a significant reduction in DVT or PE after 14 days; 14.9% of patients in the placebo group experienced DVT or PE, while the incidence was 5.5% in the LOVENOX® group ($P < 0.001$).¹⁴

During the treatment period of 14 days, a major hemorrhage was suffered by 1.1% of those who received placebo, 0.3% of those receiving 20 mg of enoxaparin daily, and 1.7% of those receiving 40 mg enoxaparin; by the end of the follow-up period (110 days), the percentages were 2.0, 1.2, and 3.4, respectively.¹⁴

In a MEDENOX subanalysis of patients with acute respiratory disease (ie, COPD exacerbation), the incidence of DVT or PE was 13.1% among placebo patients and only 3.3% among patients who received 40 mg once daily LOVENOX®, a statistically significant reduction ($P = 0.003$).¹⁵

more preservation of functional class.”

Bosentan also led to significant improvements in self-rated quality of life, and a significant reduction in serum levels of NT-probrain natriuretic peptide (NT-proBNP). The drug was well tolerated, with an adverse event profile similar to that of the placebo group.

To boost the number of patients with PAH who start treatment early, Dr. Galie suggested screening for PAH in groups that are known to have a relatively high prevalence of PAH. This includes patients with connective tissue diseases, such as scleroderma, patients infected with HIV, and patients with congenital heart disease.

Three other reports at the meeting dealt with using bosentan to treat PAH; all three studies also were sponsored by Actelion.

One study enrolled 157 patients who had a specific, relatively common form of PAH, chronic thromboembolic pulmonary hypertension (CTEPH), which was inoperable or recurrent.

The results showed that treatment with bosentan was safe and led to improvements in pulmonary vascular resistance and other measures, Dr. Irene Lang, professor of vascular biology at the Medical University of Vienna, reported at the meeting.

The Bosentan Effects in Inoperable Forms of CTEPH (BENEFIT) study randomized patients to treatment with 62.5 mg bosentan b.i.d for 4 weeks, followed by 125 mg b.i.d. for 12 weeks or placebo. Their average age was 63 years.

Bosentan was linked with a significant, 24% reduction in peripheral vascular resistance in 66 evaluable patients, compared with 71 placebo patients. Treatment also significantly boosted cardiac index, and cut NT-proBNP levels and dyspnea scores. Bosentan treatment had no significant effect on 6-minute walk distance.

Another study assessed the acute

hemodynamic effect of a single, 25-mg dose of sildenafil in 44 patients with PAH already on chronic bosentan treatment.

The results showed that the single sildenafil dose was safe, and after 60 minutes led to a significant drop in pulmonary vascular resistance, total pulmonary resistance, pulmonary artery pressure, and cardiac output.

The third study examined the pharmacokinetics of a new formulation of bosentan designed for use in children. Results from 35 patients aged 2-11 years showed that the formulation led to reasonable serum levels and a good safety profile. ■

LOVENOX® is indicated for the prophylaxis of DVT, which may lead to PE, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness

Table 3. THE-PRINCE Safety Data

	LOVENOX® n=239*	UFH n=212*	Fisher's Exact Test (2 tailed) P value
Total events (DVT or PE), n (%)	20 (8.4)	22 (10.4)	0.015
Total events among patients with severe respiratory disease	9 (7.1)	7 (5.9)	NS
Bleeding complications	5 (1.5)	12 (3.6)	NS
Hematoma at injection site (>5 cm)	24 (7.2)	42 (12.6)	0.027

NS, not significant. *Evaluable

In a Comparative Trial, LOVENOX® Had Similar Efficacy to UFH

The Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) study was a multicenter, controlled, randomized, open-label study of LOVENOX® against UFH for the prophylaxis of DVT and PE in 2 patient groups: patients with heart failure (333 randomized) and patients with severe respiratory disease (332 randomized).¹⁶

After 10±2 days of prophylaxis, there was an equivalent incidence of DVT/PE in the LOVENOX® group vs UFH (8.4% vs 10.4%, $P=0.015$) (Table 3).¹⁶ Among the patients with severe respiratory disease, the incidence of DVT/PE was 7.1% in the LOVENOX® group and 5.9% in the UFH group, a difference that was not statistically significant. Overall, there were fewer bleeding complications in the LOVENOX® group (1.5% vs 3.6% for UFH), although this difference also was not statistically significant. However, there was a significantly lower incidence of injection-site hemorrhage in the LOVENOX® group (7.2% vs 12.6% for UFH).¹⁶

Appropriate DVT/PE Prophylaxis Benefited Hospitalized Patients With Acute Respiratory Diseases Including COPD Exacerbation

Large, randomized clinical trials demonstrated that appropriate prophylaxis with LOVENOX® reduced the risk of DVT and PE in acutely ill medical patients with severely restricted mobility.^{14,16} LOVENOX® was as effective as UFH in this population and has advantages in safety and convenience.¹⁶

IMPORTANT SAFETY INFORMATION

LOVENOX® (enoxaparin sodium injection) cannot be used interchangeably with other low-molecular-weight heparins or unfractionated heparin, as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low-molecular-weight heparins or heparinoids are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of postoperative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis. Patients should be frequently monitored for signs and symptoms of neurological impairment (see boxed WARNING).

As with other anticoagulants, use with extreme caution in patients with conditions that increase the risk of hemorrhage. Dosage adjustment is recommended in patients with severe renal impairment. Unless otherwise indicated, agents that may affect hemostasis should be discontinued prior to LOVENOX® therapy. Bleeding can occur at any site during LOVENOX® therapy. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site (see WARNINGS and PRECAUTIONS).

Thrombocytopenia can occur with LOVENOX®. In patients with a history of heparin-induced thrombocytopenia, LOVENOX® should be used with extreme caution. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, LOVENOX® should be discontinued. Cases of heparin-induced thrombocytopenia have been observed in clinical practice (see WARNINGS).

The use of LOVENOX® has not been adequately studied for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves (see WARNINGS).

LOVENOX® is contraindicated in patients with hypersensitivity to enoxaparin sodium, heparin, or pork products, and in patients with active major bleeding.

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Please see a brief summary of prescribing information including boxed WARNING on the next page.

Cochrane: Ibuprofen Can Slow Lung Deterioration in CF

BY TIMOTHY F. KIRN
Elsevier Global Medical News

With careful monitoring, high-dose ibuprofen treatment can slow progressive lung damage in patients with cystic fibrosis, particularly if begun before age 13 years, according to an updated Cochrane Library review.

In the previous review, conducted 2 years ago, the same reviewers concluded that there was only preliminary evidence that nonsteroidal anti-inflammatory drugs

affected pulmonary deterioration, and they said that routine use could not be recommended. But the new review includes recent data from a large, Canadian cystic fibrosis (CF) trial conducted by one of the Cochrane reviewers—data that almost doubled the number of patients included in the latest analysis.

“High-dose ibuprofen can slow the progression of lung disease in people with CF, especially in children, and this suggests that strategies to modulate lung inflammation can be beneficial for people with

CF,” the reviewers stated.

This time, the reviewers had four trials to consider in their review, including the new Canadian one, said Dr. Larry C. Lands, director of pediatric respiratory medicine at Montreal Children’s Hospital, and his colleagues. The new study was the Trans-Canadian trial, in which 142 patients aged 6-18 years were randomized to ibuprofen treatment or placebo and were followed for 2 years (J. Pediatr. 2007;151:249-54). Dr. Lands was the lead investigator.

The primary end point of the trial was

the annual rate of decline in percent predicted forced expiratory volume in 1 second (FEV₁). Dr. Lands and his colleagues found no statistically significant difference in decline of FEV₁, although they did find apparent benefit to ibuprofen in a number of secondary end points.

In an editorial accompanying the study, Dr. Andrew Bush and Dr. Jane Davies of Royal Brompton Hospital, London, said the study authors “fail to convince us that they have shown a biologically likely benefit,” they said. The study was underpowered



Rx only
Brief Summary of Prescribing Information Rev. September 2006

SPINAL / EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage, and PRECAUTIONS, Drug Interactions).

INDICATIONS AND USAGE

- Lovenox Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism:
 - in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
 - in patients undergoing hip replacement surgery, during and following hospitalization;
 - in patients undergoing knee replacement surgery;
 - in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.
- Lovenox Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.
- Lovenox Injection is indicated for:
 - the inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium;
 - the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

See DOSAGE AND ADMINISTRATION: Adult Dosage for appropriate dosage regimens.

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection. Patients with known hypersensitivity to benzyl alcohol should not be treated using the multi-dose formulation of Lovenox.

WARNINGS

Lovenox Injection is not intended for intramuscular administration. Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

Hemorrhage:

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal. Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

Thrombocytopenia can occur with the administration of Lovenox Injection. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Pregnant Women with Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed.

Miscellaneous:

Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal “Gaspung Syndrome.” Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see PRECAUTIONS, Pregnancy).

PRECAUTIONS

General:

Lovenox Injection should not be mixed with other injections or infusions. Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Lovenox Injection should be used with care in elderly patients who may show delayed elimination of enoxaparin. If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves).

Renal Impairment:

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment. (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Low-Weight Patients:

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Laboratory Tests:

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Drug Interactions:

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfipyrazole. If co-administration is essential, conduct close clinical and laboratory monitoring (see PRECAUTIONS: Laboratory Tests).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m².

Pregnancy:

Pregnancy Category B:

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox’s potential to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations

It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis (see WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves). Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see BOXED WARNING, SPINAL/EPIDURAL HEMATOMAS). Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data:

• **Human Data** - There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.¹

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

See WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves for a clinical study of pregnant women with mechanical prosthetic heart valves.

• **Animal Data** - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cases of “Gaspung Syndrome” have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see WARNINGS, Miscellaneous).

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women.

Pediatric Use:

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

Geriatric Use:

Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (>65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger

patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered (see CLINICAL PHARMACOLOGY and General and Laboratory Tests subsections of PRECAUTIONS).

ADVERSE REACTIONS

Hemorrhage:

The incidence of major hemorrhagic complications during Lovenox Injection treatment has been low. The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection.

Indications	Major Bleeding Episodes Following Abdominal and Colorectal Surgery ¹	
	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC	Heparin 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

¹Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease \geq 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

Indications	Dosing Regimen		
	Lovenox Inj. 40 mg q.d. SC	Lovenox Inj. 30 mg q12h SC	Heparin 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis ²	n = 786 31 (4%)	n = 541 32 (6%)	
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period ³	n = 288 4 (2%)		
Extended Prophylaxis Period ⁴	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis ²		n = 294 3 (1%)	n = 225 3 (1%)

¹Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease \geq 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

²Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

³Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

⁴Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness¹

Indications	Dosing Regimen		
	Lovenox Inj. ² 40 mg q.d. SC	Lovenox Inj. ² 40 mg q12h SC	Placebo ²
Medical Patients	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

¹Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of \geq 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

²The rates represent major bleeding on study medication up to 24 hours after last dose.

Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	Lovenox Inj. ¹ 1 mg/kg q12h SC	Heparin ¹ aPTT Adjusted i.v. Therapy
Unstable Angina and Non-Q-Wave MI ^{2,3}	n = 1578 17 (1%)	n = 1529 18 (1%)

¹The rates represent major bleeding on study medication up to 12 hours after dose.

²Aspirin therapy was administered concurrently (100 to 325 mg per day).

³Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by \geq 3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment¹

Indication	Dosing Regimen		
	Lovenox Inj. 1.5 mg/kg q.d. SC	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

¹Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease \geq 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

²All patients also received warfarin sodium (dose-adjusted according to INR) to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox Injection or standard heparin therapy and continuing for up to 90 days.

Thrombocytopenia:

see WARNINGS: Thrombocytopenia.

Elevations of Serum Aminotransferases:

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox Injection should be interpreted with caution.

Local Reactions:

Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox Injection.

and failed to demonstrate a difference in its primary end point, the editorial's authors added (J. Pediatr. 2007;151:228-30).

Of the four trials analyzed in the Cochrane review, Dr. Lands and his colleagues relied mostly on the data from the Trans-Canadian trial and a 4-year trial with a similar design, which had 85 patients (N. Engl. J. Med. 1995;332:848-54). A third trial involved the use of piroxicam and could not really be compared, and the fourth trial was a dose-finding study (Cochrane Database Syst. Rev. 2007[Epub doi:10.1002/14651858.CD001505]).

Both of the trials on which the reviewers relied used twice-daily ibuprofen doses

of 20-30 mg/kg a day, up to a maximum of 1,600 mg. The doses were adjusted to produce a peak plasma concentration of 50-100 mcg/mL, because ibuprofen may actually be proinflammatory at levels below that, Dr. Lands and his colleagues said.

The Trans-Canadian trial's researchers found no statistically significant difference in the annual rate of decline in percent-predicted FEV₁, but they did find a trend. The average annual rate of decline was 1.49% in the ibuprofen-treated patients, and 2.69% in the placebo-treated patients.

The other study on which the Cochrane review focused showed a significant difference in annual FEV₁ decline: an average

percent-predicted decline of 2.17% for ibuprofen, compared with a 3.6% decline for placebo. Combining the trial data showed a difference in average decline of 1.20% in favor of ibuprofen, a difference that was "moderately" statistically significant, the reviewers said.

The second trial also demonstrated that the ibuprofen benefit was more pronounced in patients who were younger than 13 years. The average annual decline in percent-predicted FEV₁ in the younger patients was 1.49% for ibuprofen and 4.20% for placebo. In the older patients, the average annual decline was 3.13% for ibuprofen and 2.77% for placebo.

Both trials found an ibuprofen treatment benefit for forced vital capacity (FVC). The Trans-Canadian trial showed an average annual decline in percent-predicted FVC of 0.07% for ibuprofen, compared with 1.62% for placebo. The other trial demonstrated a mean annual FVC decline of 2.01% for ibuprofen, compared with 3% for placebo.

In general, the two studies showed no significant difference in intravenous antibiotics use between ibuprofen and placebo groups. However, the second study's researchers found that, in the fourth year of treatment, the percentage of patients using ibuprofen who needed intravenous antibiotic treatment was 29%, compared with 37% in the placebo group.

Dr. Lands and his colleagues noted that in the second study, a greater percentage of patients in the ibuprofen group had

THE AVERAGE ANNUAL RATE OF DECLINE WAS 1.49% IN THE IBUPROFEN-TREATED PATIENTS AND 2.69% IN THE PLACEBO-TREATED PATIENTS.

needed intravenous antibiotics before the study began (27%), and their rate of use remained relatively unchanged.

Hospital admissions for respiratory exacerbations and hospital admissions in general didn't differ between the ibuprofen and placebo groups. However, the piroxicam study suggested ibuprofen treatment decreased the number of hospitalization days by 42%. The Trans-Canadian study showed that 70 patients in the ibuprofen group were hospitalized for a total of 248 days, while the 72 patients in the placebo group were hospitalized for 561 total days.

The four trials reviewed did not explicitly report data on major hemorrhage or allergic reactions. However, in all the trials, a greater proportion of ibuprofen-treated patients reported a decrease in abdominal pain and stool frequency. Neither group showed a difference in the presence of occult blood in the stool. ■

FYI

Adult Immunization Schedule Update

The Centers for Disease Control and Prevention released its 2007-2008 Adult Immunization Schedule in English in October, and expects to release it in Spanish later this year. To download the schedule or to obtain information on other vaccine-related topics, contact the CDC by visiting www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm.

Preventive Service Recommendations

The Agency for Healthcare Research and Quality has published its 2007 "Guide to Clinical Preventive Services." It contains recommendations on 58 clinical preventive services that were made by the U.S. Preventive Services Task Force from 2001 to 2006 that can help clinicians determine which preventive medical tests are necessary for patients. To obtain copies of the guide, call 800-358-9295 or send an e-mail to ahrqpubs@ahrq.hhs.gov.

Other:

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

Adverse Event	Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients ¹ Undergoing Abdominal or Colorectal Surgery			
	Lovenox Inj. 40 mg q.d. SC n = 1228		Heparin 5000 U q8h SC n = 1234	
	Severe	Total	Severe	Total
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Ecchymosis	0%	3%	0%	3%

¹ Excluding unrelated adverse events.

Adverse Event	Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients ¹ Undergoing Hip or Knee Replacement Surgery							
	Lovenox Inj. 40 mg q.d. SC		Heparin 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC	
	Severe	Total	Severe	Total	Severe	Total	Severe	Total
Fever	0%	8%	0%	0%	<1%	5%	<1%	4%
Hemorrhage	<1%	13%	0%	5%	<1%	4%	1%	4%
Nausea	0%	16%	0%	<2%	<1%	2%	2%	5%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%
Edema	0%	6%	0%	0%	<1%	2%	<1%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%	<1%	4%

¹ Excluding unrelated adverse events.

² Data represents Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.

³ Data represents Lovenox Injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Adverse Event	Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Medical Patients ¹ With Severely Restricted Mobility During Acute Illness			
	Lovenox Inj. 40 mg q.d. SC n = 360		Placebo q.d. SC n = 362	
	Severe	Total	Severe	Total
Dyspnea	0%	3.3%	0%	5.2%
Thrombocytopenia	0%	2.8%	0%	2.8%
Confusion	0%	2.2%	0%	1.1%
Diarrhea	0%	2.2%	0%	1.7%
Nausea	0%	2.5%	0%	1.7%

¹ Excluding unrelated and unlikely adverse events.

Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction: Non-hemorrhagic clinical events reported to be related to Lovenox Injection therapy occurred at an incidence of ≤1%. Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox Injection than in patients treated with i.v. heparin. Serious adverse events with Lovenox Injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox Injection group, are provided below (irrespective of relationship to drug therapy).

Adverse Event	Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction			
	Lovenox Inj. 40 mg q.d. SC n = 1578		Heparin aPTT Adjusted i.v. Therapy n = 1529	
	Severe	Total	Severe	Total
Atrial fibrillation	11 (0.70)	3 (0.20)	11 (0.72)	11 (0.72)
Heart failure	15 (0.95)	11 (0.72)	11 (0.72)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)	11 (0.72)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)	9 (0.59)	9 (0.59)

Adverse Event	Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients ¹ Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism			
	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		Heparin aPTT Adjusted i.v. Therapy n = 344	
	Severe	Total	Severe	Total
Injection Site Hemorrhage	0%	5%	0%	<1%
Injection Site Pain	0%	2%	0%	2%
Hematuria	0%	2%	0%	<1%

¹ Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Other Ongoing Safety Surveillance Reports: Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see WARNINGS, Thrombocytopenia). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE

Symptoms/Treatment: Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg

of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products. A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSE AND ADMINISTRATION All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

Note: Lovenox Injection is available in two concentrations:

- 1. 100 mg/mL Concentration:** 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes; 300 mg / 3.0 mL multiple-dose vials.
- 2. 150 mg/mL Concentration:** 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage: Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is 40 mg once a day administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is 30 mg every 12 hours administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of 40 mg once a day SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is 40 mg once a day administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is 1 mg/kg administered SC every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In outpatient treatment, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is 1 mg/kg every 12 hours administered SC. In inpatient (hospital) treatment, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is 1 mg/kg every 12 hours administered SC or 1.5 mg/kg once a day administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.

Renal Impairment: Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS, Renal Impairment).

Indication	Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30mL/minute)	
	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy n (%)
Prophylaxis in abdominal surgery	30 mg administered SC once daily	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily	1 mg/kg administered SC once daily

Administration: Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

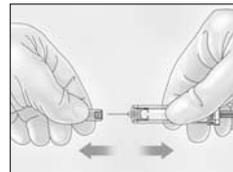
The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug. Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right antero-

LOVENOX® (enoxaparin sodium injection)

lateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



- Inject using standard technique, pushing the plunger to the bottom of the syringe.



- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



- NOTE:**
- The safety system can only be activated once the syringe has been emptied.
 - Activation of the safety system must be done only after removing the needle from the patient's skin.
 - Do not replace the needle shield after injection.
 - The safety system should not be sterilized.
 - Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

¹ Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynecol* 2001; 108 (11): 1134-40.

Sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Multiple-dose vials also manufactured by DSM Pharmaceuticals, Inc.
Greenville, NC 27835

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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Brief Summary of Prescribing Information Rev. September 2006

LOV-SEP06-B-Aa

Pulmonary Perspectives

The Perils of Pseudo-Compounded Medications

Physicians have a major responsibility to ensure the safety of their patients' medications.

Recently, there has been a significant rise in public concern about drug safety. The concern encompasses FDA-approved pharmaceuticals and, even more troubling, imported drugs that are not well regulated. Many less heavily publicized pharmaceuticals are mass-manufactured drugs prepared in the United States that masquerade as traditionally compounded products. These drugs should be of great concern to clinicians and their patients. Physicians who specialize in respiratory diseases need to be especially vigilant, because many of these medications are used in nebulizers. Hormones and dermatologic preparations are other commonly "compounded" drugs.

The age-old practice of compounding drugs is when a pharmacist prepares a pharmaceutical by mixing ingredients, in response to a physician's prescription, to meet the needs of a specific patient. This is an invaluable service rendered for patients who require special drug combinations that are not commercially available, people who may be allergic to inactive ingredients in FDA-approved products, and children who may need flavors added to encourage them to take a medicine.

However, so-called "compounding pharmacies" exist that are engaged in the mass manufacturing of drugs under the guise of a traditional compounding practice. They produce millions of doses of their product in anticipation of a physician's order. The problems with this practice are that the drugs are not FDA-approved and that the FDA does not regulate the manufacturing process. Pharmacists running these operations take the position that compounding is supposed to be regulated at a state level by state pharmacy boards. Yet the FDA can intervene, and has intervened, when it can prove that there is mass manufacturing taking place.

There are several consequences of the compounding practice that are very troubling. States do not have the resources necessary to inspect compounding pharmacies, and some states have only a handful of inspectors to cover the entire state, which allows for some extremely shoddy practices by the "compounders." The raw materials used for their preparations are not FDA-approved, so it is impossible to determine their provenance, purity, or potency. Manufacturing processes are often not sterile, and preparations have been unevenly potent, causing the overtreatment or undertreatment of patients. In addition, plastic ampules of drugs for nebulizer formulations have paper labels

with ink that can leach into the solutions, unlike FDA-approved preparations where the labeling is embossed in the plastic, to avoid this problem. There are well-documented instances of each of these problems where patient injury has resulted.

The FDA states that it knows of 200 adverse events involving 71 compounded products since 1990 (US FDA. Consumer Update, May 3, 2007: The Special Risks of Pharmacy Compounding. Available at www.fda.gov/consumer/updates/compounding053107.html), despite the fact that pharmacies are not required to report adverse events like commercial drug manufacturers. Examples of these adverse events include: (1) three patients who died of infections acquired by cardioplegic solutions during open-heart surgery; (2) two patients whose eyes were damaged by infected solutions during cataract surgery; (3) three patients who died of *Serratia*-infected injectable beclomethasone; and (4) 18 cases of *Serratia marcescens* in several states due to contaminated magnesium sulfate IV solution (Sunenshine et al. *Clin Infect Dis* 2007; 45:527). A particularly egregious and instructive case involved a Kansas City, MO, pharmacy that prepared 4,000 L of respiratory solutions to be used for nebulization and distributed them nationwide to 18,000 patients. These medications were contaminated with *Pseudomonas cepacia*. The pharmacy never notified doctors or patients about the contamination and destroyed critical records. It was ultimately disciplined by the state Board of Pharmacy, which, in Missouri, is more aggressive and effective than in many other jurisdictions (Missouri Board of Pharmacy Takes Action Against Kansas City Company [press release]. Jefferson City, MO, March 10, 2003).

In some instances, "compounding" manufacturers claim that they have generic versions of drugs, which are, in fact, not FDA-approved; therefore, they are not available in this country. An example is the medication budesonide, for use in nebulizers. The only approved form of this drug is Pulmicort Respules (AstraZeneca; Wilmington, DE), a special formulation that is aqueous-soluble. Budesonide is notoriously insoluble in water, so these "compounders" dissolve it in high concentrations of ethanol. Their preparations are then sold and administered to patients, including children, via nebulization. Ethanol is very irritating to the lungs and, in these cases, is being given to patients who already have inflammatory lung disease.

These drugs are marketed in ways that are deceptive to physicians and patients. In one marketing method, suppliers of durable medical equipment link up with the mass manufacturers. When a patient

submits an order for a nebulizer, the supplier will offer a free nebulizer if the patient gets his medication from the supplier, which is delivered to his home. The supplier bills the insurance company or Medicare, and the medication is virtually cost-free. This sounds like a good deal, except for the fact that the medications are unreliable and can even be dangerous.

Physician approval for compounded drugs may also be obtained deceptively. The request for approval is faxed to the physician from the pharmacy; however, frequently, the form does not make it clear that a substitution is being requested. In addition, the form does not indicate that these drugs are not FDA-approved, and that many other combination drugs offered are available in FDA-approved versions. A major example of this is the albuterol/ipratropium combination, available as DuoNeb (Dey, L.P.; Napa, CA), which seems to be a favorite of mass manufacturers. Another example is budesonide,

as previously noted. Physicians may be unaware that they are signing off on drugs that are not FDA-approved and of inferior quality. One could speculate that the "compounding" manufacturers and distributors are counting on physicians being too busy to scrutinize what they are signing.

Is there any peril to physicians if a patient becomes ill as a result of taking such a medicine? In fact, it is the physician who becomes liable for the adverse events. Once the physician approves the medication, the pharmacist preparing the drug is no longer at risk for liability.

One might ask what is being done to protect patients and physicians from these unscrupulous pharmacies. The FDA issued a Compliance Policy Guide in 2002 outlining the circumstances that would trigger its intervention. To the extent the FDA can intervene with limited resources, it has intervened. This list also is instructive in identifying the behaviors of these pharmacies that put them in conflict with proper manufacturing practices. These behaviors include:

- ▶ Compounding drug products that have been pulled from the market because they were found to be unsafe or ineffective.
- ▶ Compounding drugs that are essentially copies of a commercially available drug.
- ▶ Compounding drugs in advance of receiving prescriptions, except in very limited quantities relating to the amounts of drugs previously compounded based on valid prescriptions.
- ▶ Compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs, without an FDA-sanctioned, investigational new drug application.

▶ Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.

▶ Failing to conform to applicable state law regulating the practice of pharmacy (US FDA. Consumer Update, May 3, 2007: The Special Risks of Pharmacy Compounding. Available at www.fda.gov/consumer/updates/compounding053107.html).

Compounding has been a major concern for patient advocacy groups and specialty societies. Allergy and Asthma Network/Mothers of Asthmatics took the lead in forming a coalition of patient groups, specialty societies, and pharma-

ceutical companies to address this problem. The coalition, called Consumer Health Alliance for Safe Medications, has helped raise public awareness through lobbying, education programs, and media events. It has brought the problem to the attention of the Centers for Medicare

and Medicaid Services and, as a result, Medicare is no longer providing reimbursement for medications not approved by the FDA. Attempts to secure federal legislation are ongoing.

Consumers can protect themselves by ensuring that the medication they get from pharmacies or durable medical equipment companies is FDA-approved. They should check with their physicians and pharmacies.

Physicians have a major responsibility to ensure the safety of their patients' medications. They must read all their faxes for prescriptions before they sign them. They also need to read the fine print to ensure that the concentrations of combination medications are the same as in their commercial preparations. They must insist that the medications they prescribe are dispensed as written and their patients' medications are FDA-approved. They need to be aware that, if their patients are not doing well using their nebulized medication, the problem could be that the medication was obtained from a compounding pharmacy and underpotent.

Physicians must insist that whatever medication their patients inhale, ingest, or apply, it conforms to the highest possible manufacturing standards and that "compounded" products are not surreptitiously substituted for FDA-approved medications. ■

Dr. Daniel Ein
Chief, Division of Allergy
and Clinical Professor of Medicine
George Washington University
School of Medicine
Washington, DC



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PRESIDENT'S REPORT

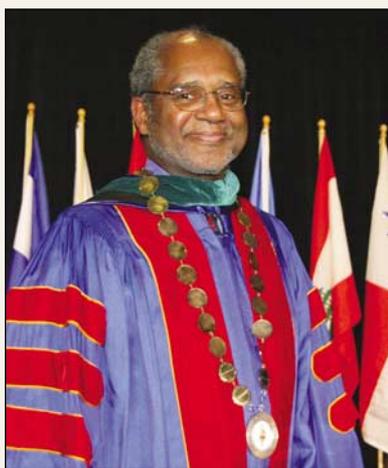
Welcoming a New ACCP President

Dr. Alvin V. Thomas, Jr., FCCP, assumed the role of ACCP President during Convocation ceremonies at CHEST 2007.

Dr. Thomas is Associate Professor of Internal Medicine and Pulmonary Medicine and Chief of the Pulmonary Division at Howard University in Washington, DC.

He also serves as Graduate Faculty Representative on the Howard University Board of Trustees.

Dr. Thomas has been a member



DR. ALVIN V.
THOMAS, JR., FCCP

of the ACCP since 1973 and has been active in ACCP leadership, serving on several committees, including the Continuing Education Committee.

In addition, he was a Trustee of The CHEST Foundation (1999-2003), Chair of the ACCP Scientific Program and Abstracts Committee (2000-2001), and Scientific Program Chair for CHEST 2002.

His scholarly and research interests are in pulmonary vascular disease, particularly sickle cell acute chest syndrome and pulmonary hypertension in sickle cell disease.

We asked Dr. Thomas to briefly discuss some of his plans for the upcoming presidential year.

Q. What would you like to accomplish as President of the ACCP?

I intend to focus on the issue of disparities in health and health care, particularly among minorities and the poor and underserved in this country.

These are issues that are being increasingly discussed at a national level and in the general medical literature, but there has been minimal discussion of the

issues in the pulmonary, critical care, and sleep literature.

My goal is to have the issue of disparities be a part of the "cultural fabric" of the College. The issue is relevant to all ACCP activities—

education, research, and advocacy.

An additional goal is to have the ACCP (and The CHEST Foundation) become national thought leaders on disparity issues in pulmonary, critical care, and sleep medicine.

Q. What do you consider to be the greatest strengths of the ACCP and how will you build upon them?

By far, the greatest strengths of the College are the members and the staff (including the executive

Rozerem

ramelteon 8-mg tablets

Brief Summary of Prescribing Information

ROZEREM™ (ramelteon) Tablets

INDICATIONS AND USAGE

ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS

ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program. ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM. After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS

General

ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations. Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children

ROZEREM has been associated with an effect on reproductive hormones in adults, e.g., decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see **Pediatric Use**).

Information for Patients

Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed. Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM. Patients should be advised that they should not take ROZEREM with or immediately after a high-fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females; decreased libido, or problems with fertility.

Laboratory Tests

No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions

ROZEREM has a highly variable intersubject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C3 subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism

Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the AUC_{0-12h} for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (see **WARNINGS**). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both AUC_{0-12h} and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The AUC_{0-12h} and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure (AUC_{0-12h} and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs

Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem

Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of Sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions

ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study, B6C3F₁ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥ 100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area under the concentration-time curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 50, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24-hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK⁺ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m² basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m² basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m² basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m² basis) when considering all studies.

Pregnancy: Pregnancy Category C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose (MRHD) on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area under the concentration-time curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were

studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and post-natal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m² basis).

Labor and Delivery

The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers

Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use

A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS

Overview

The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment

Six percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials

The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%).

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 clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE

ROZEREM is not a controlled substance.

Human Data: See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents, in the Complete Prescribing Information.

Animal Data: Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotarod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotarod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE

Signs and Symptoms

No cases of ROZEREM overdose have been reported during clinical development. ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdose is not appropriate.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdosage.

Rx only

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Manufactured in:
Takeda Ireland Ltd.
Kilruddery, County Wicklow, Republic of Ireland

Marketed by:
Takeda Pharmaceuticals America, Inc.
One Takeda Parkway
Deerfield, IL 60015

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NEWS FROM THE COLLEGE

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management). Since my very first time of involvement with the College, I have been totally impressed with the professionalism, dedication to excellence, motivation, and willingness to help that the entire staff (without exception) has shown.

My experience has been the same with the College's executive management, including the Executive Vice President and CEO, who sets the

expectations and standards for the organization.

Over the years, as I have been increasingly involved in leadership activities within the ACCP, I have experienced the same attitude of dedication and commitment by members of the College.

Whenever a specific task needs to be completed, without exception, a member (or members) steps forward to

volunteer his or her time and talent, despite a full plate of commitments at home base.

I have never worked with any other organization where people so willingly volunteer their time and talent.

This culture of service to the College, by staff and members, is what makes the ACCP so special and so successful. It is truly a "family."

Q. What is the greatest challenge facing the College and how will you address it?

The challenges that the College faces are several, including the issue of standards of quality medical care for the profession and the evaluation of physician medical care and pay for performance.

However, among the most urgent is the nature and role of medical education in our discipline, including adherence to increasingly stringent continuing medical education guidelines by the Accreditation Council for Continuing Medical Education (ACCME).

Associated with this issue is the nature of our changing relationship with the pharmaceutical industry.

These two later issues have and will have enormous impact on the nature and financial support of the College's educational efforts.

The College's Education Committee has developed and continues to develop innovative approaches to many of the ACCME guidelines. Several are being implemented at CHEST 2007. College staff and physician leadership are actively involved with efforts to respond to ACCME guidelines on pharmaceutical support.

I will be discussing these and other issues in future editions of our *CHEST Physician* newspaper.

Q. And finally, what is your charge to the members and new Fellows of the ACCP?

My charge to members and new FCCPs is to get involved in the activities of the College. Join a NetWork of your choice. Participate in the many educational opportunities offered by the College (including board reviews and educational courses), and attend annual CHEST meetings, including CHEST 2008 in Philadelphia.

The ACCP is a dynamic and responsive organization. Make us part of your professional life. ■

You can prescribe Rozerem for as long as you need to*



Clinical studies show no evidence of potential abuse, dependence, or withdrawal†

- **First and only**—nonscheduled prescription insomnia medication...not a controlled substance and can be prescribed for long-term use¹
- **First and only**—prescription insomnia medication that targets the normal sleep-wake cycle¹
- **First and only**—prescription insomnia medication with no evidence of abuse potential in clinical studies¹
- **First and only**—prescription insomnia medication that does not promote sleep by CNS depression¹
- **One simple 8-mg dose**¹

†Rozerem is not a controlled substance. A clinical abuse liability study showed no differences indicative of abuse potential between Rozerem and placebo at doses up to 20 times the recommended dose (N=14). Three 35-day insomnia studies showed no evidence of rebound insomnia or withdrawal symptoms with Rozerem compared to placebo (N=2082).^{1,2}

Please visit www.rozerem.com

*Rozerem™ (ramelteon) is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use.

Important safety information

Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Avoid taking Rozerem with alcohol. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

Rozerem™
ramelteon 8-mg tablets

Proven for sleep.
Nonscheduled for added safety.



EDUCATION INSIGHTS

Publishing and Promoting Evidence-Based Guidelines

BY DR. SANDRA
ZELMAN LEWIS

ACCP Assistant Vice President,
Health and Science Policy

The Health and Science Policy (HSP) Committee and ACCP staff have had a prolific 2007 and anticipate more publications in 2008. Three evidence-based clinical practice guidelines were published in the current year, along with a policy paper. Next year will see the publication of several more guidelines. In addition, the ACCP had a chance to promote our guideline development work at an international conference this past summer.

In May, *Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Guidelines* was published as a supplement to *CHEST*. Dr. Andrew Reis, FCCP, chaired the panel of nine authors and one methodologist. The importance of pulmonary rehabilitation in the care and management of patients with COPD has grown as the scientific literature on this topic has expanded, leading to the need for a set of guidelines.

Under the supervision of the guideline chair, Dr. Lewis Rubin, FCCP, "Pulmonary Arterial Hypertension Medical Therapies Update" was published in June's issue of *CHEST* to incorporate important recent evidence and revise the recommendations and medical treatment algorithm from the 2004 supplement, *Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines*.

The *Diagnosis and Management of Lung Cancer: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (2nd Edition)* was published in September as a supplement to *CHEST*. Dr. Michael Alberts, FCCP, and Dr. Gene Colice, FCCP, led a panel of nearly 100 multidisciplinary lung cancer experts. The Evidence-Based Practice Center at Duke University performed the literature review and analyses to guide the development of the recommendations in five treatment areas. In addition, five areas that received the *de novo* review in the first edition were updated with new literature and revised recommendations. Three new chapters address pathology, integrative oncology, and bronchioloalveolar lung cancer. These guidelines received considerable media attention in both the lay and medical press. Dr. Robert Milroy penned an editorial that was published in the same month's issue of *CHEST*:

"The ACCP lung cancer guideline project group most certainly have achieved their goal to produce updated, evidence-based, clinically relevant guidelines for physicians and other healthcare providers managing the care of patients with lung cancer and those who

are at risk for lung cancer. There is no doubt that publication of the Second Edition of these lung cancer guidelines ... represents an important addition to the lung cancer guidelines armamentarium, and will result in further improvements in the processes of care,

treatments, and outcomes for lung cancer patients, not only in the United States but throughout the rest of the world."

Continuing in the tradition of publicizing HSP processes and advancements, "ACCP Evidence-Based Guideline Development: A



XOLAIR IS INDICATED FOR: Adults and adolescents (aged ≥ 12 years) with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. XOLAIR has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

WARNING: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after XOLAIR administration, and health care providers administering XOLAIR should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see WARNINGS, and PRECAUTIONS, Information for Patients).

NEWS FROM THE COLLEGE

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Successful and Transparent Approach Addressing Conflict of Interest, Funding, and Patient-Centered Recommendations” was published online in May and in print in September in *CHEST*. This paper proffers the key HSP processes from topic submission to dissemination of the final products. This ACCP guideline development methodology, forever a work-in-progress, received praise in an accompanying editorial by Dr. Carolyn Clancy, the

Director of the Agency for Healthcare Research and Quality (AHRQ), and Jean Slutsky, PA, MSPH, the Director, Center for Outcomes and Evidence, AHRQ.

Dr. Ian Nathanson, FCCP, and Dr. Sandra Zelman Lewis attended the Guidelines International Network (GIN) meeting in Toronto, Ontario, Canada, in August. This was the first time this international group met on the North American continent. Dr. Nathanson

displayed a poster and addressed questions from a thoughtful audience about an implementation project at the Nemours Clinic utilizing the ACCP grading system. Dr. Lewis presented a session on the ACCP guideline development process, which was well received by this international community of evidence-based medicine scholars.

Looking forward, HSP is anticipating the publication of several guidelines in

2008, including the following:

- ▶ 8th edition of the Antithrombotic and Thrombolytic Guidelines
- ▶ A new topic, Management of Dyspnea in Advanced Lung Disease and Congestive Heart Failure
- ▶ The first nonclinical guideline topic, Continuing Medical Education

For more information about the HSP projects and products, contact Dr. Sandra Zelman Lewis at slewis@chestnet.org. ■

For allergic asthma patients who remain symptomatic on conventional therapies including ICS*...

Capture IgE
And interrupt signals that may
lead to asthma attacks.†

Test for total IgE. Treat with XOLAIR.

*Inhaled corticosteroids.

†XOLAIR on average inhibits 96% of IgE from binding to the high-affinity IgE receptor on the surface of mast cells and basophils.¹

IMPORTANT SAFETY INFORMATION

XOLAIR should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. XOLAIR should not be administered to patients who have experienced a severe hypersensitivity reaction to XOLAIR (see Boxed WARNING). XOLAIR should be discontinued in patients who experience a severe hypersensitivity reaction. Malignant neoplasms were observed in 20 of 4127 (0.5%) XOLAIR-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. Patients should be given and instructed to read the Medication Guide before starting treatment and before each subsequent treatment. Patients receiving XOLAIR should be told not to decrease the dose of, or stop taking, any other asthma medications unless otherwise instructed by their physician. The adverse reactions most commonly observed among patients treated with XOLAIR in clinical studies included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in XOLAIR-treated patients and control patients.

Xolair
Omalizumab

FOR SUBCUTANEOUS USE

Anti-IgE therapy that helps protect

NETWORKS

Of Surveys, Stents, and CMS Challenges

Affiliate

The goal of the Affiliate NetWork is to provide an avenue for presentation at national meetings, leadership opportunities within the ACCP, and direction for both education and career development. ACCP

Affiliate membership is available to all physicians-in-training who have been accepted to, or are currently participating in, a fellowship, residency, or equivalent program of clinical cardiopulmonary medicine, surgery, critical care, sleep, or one of

the closely related specialties. Membership dues are discounted to allow all interested physicians-in-training to participate.

At CHEST 2007, there were 146 scheduled case presentations, following a record 367 submissions. All presentations are

moderated by an Affiliate member and feature a guest expert in the particular area of focus. Also at CHEST 2007, two Affiliate members were given the opportunity to participate in "Stump the Stars," a session conducted in a clinical/radiologic/pathologic case report format. Dr. Julian Williams from Coney Island Hospital in Brooklyn, NY, and Dr. Nazar Almakki from Howard University Hospital in Washington, DC, were selected to present interesting, unknown cases to esteemed professors Dr. Marvin Schwarz, FCCP, and Dr. Jeffrey Myers, FCCP.

Ideas for NetWork activities and Web page content (www.chestnet.org/networks/affiliate/) are welcomed and can be e-mailed to networks@chestnet.org.

Airways Disorders

In mid-2006, the US Food Drug Administration (FDA) posted a "black-box" warning on the use of long-acting beta-agonists (LABAs), based on data that suggested there could be an increase in mortality when certain populations receive this medication. The Airways Disorders NetWork embarked on a project to obtain information about what US physicians understand about the potential risks and benefits of LABA use for their patients, as well as to understand the LABA-prescribing patterns across various groups of physicians. The NetWork recently designed and distributed a survey to more than 8,000 practicing physicians. The working group, chaired by Dr. Jill Karpel, FCCP, plans to prepare an abstract and distribute the findings in the coming months. For more information about the Airways Disorders NetWork, send an e-mail to networks@chestnet.org.

Interventional Chest/Diagnostic Procedures

Central airway obstruction is a devastating process caused by both malignant and benign etiologies. The development of self-expanding metallic airway stents (SEMS) made this therapy available to a wider population of pulmonologists.

Coincident with the advancing technology, multiple publications revealed the significant and immediate benefits for many patients. The results were inspiring, but complications always exist. There has been a history of concern about the risk-to-benefit ratio of SEMS in patients with benign airways disease. Removal of long-standing metallic stents is known to be problematic and associated with serious complica-



BRIEF SUMMARY

Please see package insert for Full Prescribing Information.

WARNING

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair administration, and health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur (see WARNINGS, and PRECAUTIONS, Information for Patients).

INDICATIONS AND USAGE

Xolair (Omalizumab) is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

CONTRAINDICATIONS

Xolair should not be administered to patients who have experienced a severe hypersensitivity reaction to Xolair (see WARNINGS: Anaphylaxis).

WARNINGS

Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Xolair should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports (see ADVERSE REACTIONS). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur (See PRECAUTIONS, Information for Patients).

Xolair should be discontinued in patients who experience a severe hypersensitivity reaction (see CONTRAINDICATIONS).

Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known.

PRECAUTIONS

General

Xolair has not been shown to alleviate asthma exacerbations acutely and should not be used for the treatment of acute bronchospasm or status asthmaticus.

Corticosteroid Reduction

Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy. Decreases in corticosteroids should be performed under the direct supervision of a physician and may need to be performed gradually.

Information for Patients

Patients receiving Xolair should be told not to decrease the dose of, or stop taking any other asthma medications unless otherwise instructed by their physician. Patients should be told that they may not see immediate improvement in their asthma after beginning Xolair therapy.

Parasitic (Helminth) Infection

In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminth infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Omalizumab-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Omalizumab than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups. Patients at high risk of geohelminth infection should be monitored for such infections while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair-IgE complexes. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Serum total IgE levels obtained less than 1 year following discontinuation may not reflect steady state free IgE levels and should not be used to reassess the dosing regimen.

Drug Interactions

No formal drug interaction studies have been performed with Xolair. The concomitant use of Xolair and allergen immunotherapy has not been evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair. No evidence of mutagenic activity was observed in Ames tests using

six different strains of bacteria with and without metabolic activation at Omalizumab concentrations up to 5000 µg/mL.

The effects of Omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of Omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation, in female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Pregnancy (Category B)

Reproduction studies in cynomolgus monkeys have been conducted with Omalizumab. Subcutaneous doses up to 75 mg/kg (12-fold the maximum clinical dose) of Omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing.

IgG molecules are known to cross the placental barrier. There are no adequate and well-controlled studies of Xolair in pregnant women. Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Pregnancy Exposure Registry

To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established. Healthcare providers should encourage their patients to call 1-866-4XOLAIR (1-866-496-5247) to enroll in the Xolair Pregnancy Exposure Registry. Healthcare providers can call this number to obtain further information about this registry.

Nursing Mothers

The excretion of Omalizumab in milk was evaluated in female cynomolgus monkeys receiving SC doses of 75 mg/kg/week. Neonatal plasma levels of Omalizumab after *in utero* exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Milk levels of Omalizumab were 1.5% of maternal blood concentration. While Xolair presence in human milk has not been studied, IgG is excreted in human milk and therefore it is expected that Xolair will be present in human milk. The potential for Xolair absorption or harm to the infant are unknown; caution should be exercised when administering Xolair to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use

In clinical trials 134 patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is insufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

Clinical Trials Experience

The most serious adverse reactions occurring in clinical trials with Xolair were anaphylaxis and malignancies (see WARNINGS). Anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient.

In clinical trials the observed incidence of malignancy among Xolair-treated patients (0.5%) was numerically higher than among patients in control groups (0.2%).

The adverse reactions most commonly observed among patients treated with Xolair in clinical studies included injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients. These were also the most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse reaction).

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

The data described above reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

Table 1 shows adverse events that occurred $\geq 1\%$ more frequently in patients receiving Xolair than in those receiving placebo in the placebo-controlled asthma studies. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 1.

Adverse event	Table 1 Adverse Events $\geq 1\%$ More Frequent in Xolair-Treated Patients	
	Xolair n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

Age (among patients under age 65), race, and gender did not appear to affect the between group differences in the rates of adverse events.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection-site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

Immunogenicity

Low titers of antibodies to Xolair were detected in approximately 1/1723 (<0.1%) of patients treated with Xolair. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in an ELISA assay and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

Postmarketing Spontaneous Reports

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown. Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only. Hematologic: Severe thrombocytopenia has been reported in postapproval use of Xolair.

Skin: Hair loss has been reported in postapproval use of Xolair.

OVERDOSAGE

The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period, which was not associated with toxicities.

MEDICATION GUIDE

XOLAIR®
(OMALIZUMAB)

**IMPORTANT: XOLAIR SHOULD ALWAYS BE INJECTED
IN YOUR DOCTOR'S OFFICE.**

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XOLAIR?

A severe allergic reaction called anaphylaxis has happened in some patients after they received Xolair. Anaphylaxis is a life-threatening condition and can lead to death so get emergency medical treatment right away if symptoms occur.

Signs and Symptoms of anaphylaxis include:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Get emergency medical treatment right away if you have signs or symptoms of anaphylaxis after receiving Xolair.

Anaphylaxis from Xolair can happen:

- right after receiving a Xolair injection or hours later
- after any Xolair injection. Anaphylaxis has occurred after the first Xolair injection or after many Xolair injections.

Your healthcare provider should watch you for some time in the office for signs or symptoms of anaphylaxis after injecting Xolair. If you have signs or symptoms of anaphylaxis, tell your healthcare provider right away. Your healthcare provider should instruct you about getting emergency medical treatment and further medical care if you have signs or symptoms of anaphylaxis after leaving the doctor's office.

WHAT IS XOLAIR?

Xolair is an injectable medicine for patients ages 12 and older with moderate to severe persistent allergic asthma whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids. A skin or blood test is done to see if you have allergic asthma.

WHAT ELSE SHOULD I KNOW ABOUT XOLAIR?

- You should not receive Xolair if you have ever had an allergic reaction to a Xolair injection.
- Do not change or stop taking any of your other asthma medicines unless your healthcare provider tells you to do so.
- There are other possible side effects with Xolair. Talk to your doctor for more information. You can also go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Revision Date: July 2007

NEWS FROM THE COLLEGE



tions. These issues led the FDA to publish an advisory on the use of metallic stents in patients with "benign airway disorders" in 2005 (US Food and Drug Administration Web site. Available at: www.fda.gov/cdrh/safety/072905-tracheal.html. Accessed September 18, 2007).

The FDA advisory recommended that physicians always review the indications, warnings, and precautions for appropriate patient selection. Metallic tracheal stents should be used in patients with benign airway disorders only after thoroughly exploring all other options. Bridging therapy with metallic tracheal stents is not recommended, because removal of the metallic stent can result in serious complications. If a metallic tracheal stent is the only option for a patient, insertion should be done by a physician who is experienced in metallic stent placement and removal. If removal is necessary, the procedure should be performed by a physician who is experienced in removing metallic stents.

The ACCP Interventional Chest/Diagnostic Procedures NetWork Steering Committee recently prepared and published an editorial addressing this issue.

The editorial, "Airway Stenting for Patients With Benign Airway Disease and the FDA Advisory: A Call for Restraint," was published in *CHEST* (2007; 132:1105) and fully supports the FDA advisory. The NetWork Steering Committee believes that all physicians who utilize endoluminal airway therapies should be familiar with the ACCP and the American Thoracic Society/European Respiratory Society consensus statements (see "Recommended Reading" below).

Unfortunately, there are no consensus suggestions for the use of SEMS in patients with benign central airway obstruction.

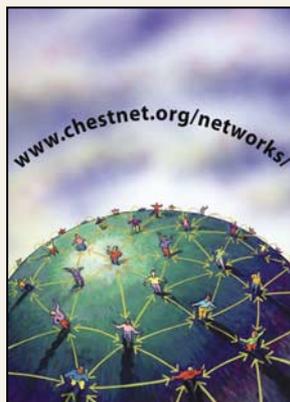
Dr. Mark E. Lund, FCCP
Interventional Chest/Diagnostic Procedures
Steering Committee Member

Recommended Reading

1. Ernst A, Silvestri GA, Johnstone D, et al. Interventional pulmonary procedures:

guidelines from the American College of Chest Physicians. *Chest* 2003; 123:1693-1717

2. Bolliger CT, Mathur PN, Beamis JF, et al. ERS/ATS statement on interventional pulmonology. *European Respiratory Society/American Thoracic Society. Eur Respir J* 2002; 19:356-373



Pulmonary Physiology, Function, and Rehabilitation

On June 27, 2007, the Centers for Medicare & Medicaid Services announced that it did not have the statutory authority to cover pulmonary rehabilitation programs. One month

later, the US House of Representatives' Committee on Ways and Means and Committee on Energy and Commerce recommended Medicare legislation that does not include HR 552, a bill that would formally establish pulmonary and cardiac rehabilitation as a Medicare benefit. The Senate has S 329, a bill identical

to the House bill HR 522, which has gained significant sponsorship from at least 33 members of the Senate. At the time of this writing, a final decision regarding the bill is still pending. Members of the NetWork, along with members of the Government Relations Committee, have been working with members of other organizations, including the American Thoracic Society, the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), and NAMDRRC, to attempt to gain further support for this Senate bill.

The Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines were published in the May 2007 issue of *CHEST* (2007; 131:4S). These guidelines were a project originating with the NetWork and include an update of the 1997 guidelines, as well as new guidelines on the topics of exercise maintenance following pulmonary rehabilitation, nutrition, supplemental oxygen therapy, and diseases other than COPD. These guidelines further strengthen the scientific basis for the effectiveness of pulmonary rehabilitation. ■

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ACCP Fellow Is Named New Dean of LSU Medical School

Dr. Steve Nelson, FCCP, has been appointed the new Dean of the School of Medicine of the

Louisiana State University Health Sciences Center in New Orleans by Center Chancellor Dr. Larry Hollier.

Joining the faculty in 1984, Dr. Nelson was named as Professor of Medicine in 1994 and the John H. Seabury Professor of Medicine in 1995. Since 2000, Dr. Nelson has served as Director of one of only five National Institutes of Health-awarded comprehensive alcohol research centers in the nation. He served as Vice-Chair of Research in the Department of Medicine and was named Chief of the Section of Pulmonary Medicine in 2005.

Dr. Nelson's major clinical interests

include lung immunology, pneumonia, adult cystic fibrosis, and sepsis. His research interests are primarily directed



**DR. STEVE
NELSON, FCCP**

toward understanding normal pulmonary host defense mechanisms; defining how disease states undermine and disrupt these defense mechanisms; and determining the potential of biological response modifiers, including gene therapy, to provide innovative approaches to the prevention and treatment of pulmonary infections.

Dr. Nelson received the 2006 Edward C. Rosenow III, MD, Master FCCP Honor Lecture Award from the ACCP for outstanding contributions to mentorship and training of chest physicians. He also is a reviewer for *CHEST* and several other medical journals. ■

Product of the Month: PCCU

In the two new second editions of *Best of PCCU*, you will find some of the best critical care and pulmonary articles from recent PCCU volumes to provide you with current information and management strategies related to the care of critically ill and pulmonary patients.

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In the critical care and pulmonary editions, several of these lessons have been updated with new material and references, including the addition of the ACTH (Cortrosyn) stimulation test to the low systemic vascular resistance lesson in the critical care

edition and the addition of the AASM scoring guidelines to the polysomnography lesson in the pulmonary edition.

Each article ends with poststudy questions, so you can test your comprehension and compare your results to the correct responses found at the end of the book.

The ACCP is certain that the current information and management strategies presented in the second updated editions of the *BEST of PCCU Critical Care* and the *Best of PCCU Pulmonary* will enhance the care you provide for your patients.

For more information and to purchase the newly updated *Best of PCCU* editions, please visit the ACCP Store online at www.chestnet.org and click on the ACCP Store icon, at the top right side of the page. ■



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December 6 - 9, 2007

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SBPT/ACCP
Araxa, Brazil

December 7 - 9, 2007

Ultrasonography:
Fundamentals in
Critical Care
Scottsdale, Arizona

January 10 - 13, 2008

Sleep Medicine 2008
Scottsdale, Arizona

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Ultrasonography:
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May 9 - 10, 2008

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NEWS FROM THE COLLEGE



SLEEP STRATEGIES

Portable Monitoring for Sleep Apnea: An Update

The diagnosis of sleep apnea, once a relatively straightforward proposition, is getting more complicated each year.

In the past, polysomnography was the only test available for diagnosing sleep apnea. However, over the last decade, recording technology has advanced to where it is relatively easy to make high quality recordings of multiple physiologic signals simultaneously in just about any setting, including the home. The use of this technology is slowly changing the discussions about sleep apnea, if not the face of the disease quite yet.

For the last 10 years, portable testing for sleep apnea has been “just around the corner.” The future may be coming soon, depending on the results of a meeting held September 12, 2007, at the headquarters of the Centers for Medicare & Medicaid Services (CMS) in Baltimore, MD.

At the present time, sleep apnea must be diagnosed in a sleep laboratory facility in order for the subsequent provision of continuous positive airway pressure (CPAP) therapy to be reimbursed by insurers.

This has always been the position of Medicare. Most private insurers institute their policies according to the large federal insurer. This means that most insurers will not pay for CPAP therapy on the basis of sleep apnea diagnosed with a portable sleep apnea monitor in a patient's home.

Over the last decade, sleep recording equipment manufacturers have developed portable sleep apnea monitors that many physicians in the sleep apnea field believe are sufficiently accurate for use, at least in some cases, in diagnosing sleep apnea outside of a sleep laboratory setting.

CMS last examined this issue in 2004. At that time, CMS asked its Medical Care Advisory Committee (MCAC) to consider adopting new rules that would allow CPAP to be paid for by Medicare and Medicaid based on a portable sleep study performed outside of a sleep laboratory facility.

At this 2004 meeting, the MCAC did not recommend approval to this requested change in CMS regulations. The MCAC did encourage those individuals in the sleep apnea field to continue to develop a higher quality of evidence showing the benefits of portable sleep apnea monitors, especially in the elderly and those who are disabled—groups of patients CMS typically serves.

Fast forward to 2007: At the request

of the American Academy of Otolaryngology, CMS decided to revisit this question. The MCAC was asked to consider expanding CMS regulations to include CPAP coverage for Medicare beneficiaries when the diagnosis is based on a non-facility-based sleep study.

To analyze this topic further, the Agency for Healthcare Research and Quality commissioned a state-of-the-science review from the Evidence-Based Practice Center (EPC) at Tufts–New England Medical Center.

The work of the EPC work was completed in early 2007 and distributed to various reviewers and stakeholders for comment. Many readers interpreted the comments as giving a cautiously optimistic view of portable sleep apnea monitoring with level 3 monitors, which are capable of recording airflow, respiratory effort, pulse-oximetry, and heart rate.

On behalf of the ACCP, Dr. Richard Castriotta, FCCP (Chair, Sleep Medicine NetWork) and I (Chair, Sleep Institute) attended the CMS meeting. We prepared comments for the meeting several weeks prior to attending.

Our position was similar to the position the ACCP has held since the first MCAC meeting in 2004. We stated that the ACCP was in favor of expanding non-facility-based testing with certain precautions in place to prevent misuse of the technology.

We told the MCAC, and at least 70 attendees, that “our goal is not to turn every bedroom in America into a sleep laboratory,” but that thoughtful and careful use of portable sleep apnea testing may improve the availability of testing for patients with a high likelihood of obstructive sleep apnea. These patients may not have a sleep laboratory available for testing or insurance coverage for sleep laboratory services.

Our comments also stressed the importance of restricting the use of portable sleep apnea testing to physicians who are knowledgeable about sleep apnea and appropriately trained in the use of these devices. We also stressed the need for making facility-based sleep laboratories available for patients who have equivocal or nondiagnostic studies.

Others at the MCAC meeting took a similar position. The American Thoracic Society emphasized the need for more research on alternative ways of diagnosing sleep apnea and initiating therapy, stating that portable sleep apnea monitoring was promising but not completely proven. The American

Academy of Otolaryngology, which initiated this request for review of current CMS policy, came out strongly in favor of portable monitoring, as did several speakers associated with various portable testing technologies or patient advocacy groups. The National Association for Medical Direction of Respiratory Care (NAMDR) supported increasing coverage for portable monitors, as well as some needed changes to current polysomnography policy.

As was the case at the 2004 MCAC meeting, the American Academy of Sleep Medicine (AASM) presented the view that portable testing is not ready for widespread use; therefore, CMS should make no change to the current regulations. The foundation of the AASM has initiated a study examining one particular approach to portable monitoring and recommends waiting until that study is completed.

After comments were heard and a

brief general discussion was held, in which the MCAC members asked questions of the speakers and the audience, the committee members voted on a series of questions about the possible role of portable sleep apnea testing developed by CMS prior to the meeting.

My impression of the MCAC deliberation was that they were interested in the *idea* of portable sleep apnea testing but had concerns about how it could be put into practice.

It was clear from their subsequent open discussions that they were impressed with a recent study published earlier this year by Mulgrew and colleagues (Mulgrew et al. *Ann Intern Med* 2007;147:157) from the University of British Columbia. The study compared clinical outcomes from a cohort of patients with rather severe sleep apnea, who were randomly assigned to either traditional in-lab diagnosis and treatment or autotitrating CPAP,

Continued on following page

Sleep Institute

American College
of Chest Physicians

(Chair, Sleep Institute) attended the CMS meeting. We prepared comments for the meeting several weeks prior to attending.

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

- ▶ **Family Satisfaction in the ICU: Differences Between Families of Survivors and Nonsurvivors.** *By Dr. R. J. Wall, et al.*
- ▶ **Daytime Cheyne-Stokes Respiration in Ambulatory Patients With Severe Congestive Heart Failure Is Associated With Increased Mortality.** *By Dr. T. Brack, FCCP, et al.*
- ▶ **Topics in Practice Management: Split-night Polysomnography.** *By Dr. N. P. Patel, et al.*
- ▶ **Portable Monitors in the Diagnosis of Obstructive Sleep Apnea.** *By Dr. M. Ahmed, et al.*
- ▶ **Recent Advances in Chest Medicine: Preoperative Evaluation of the Patient With Pulmonary Disease.** *By Dr. S. R. Bapojé, et al.*
- ▶ **Organ Allocation in Lung Transplant.** *By Dr. S. Q. Davis; and Dr. E. R. Garrity, Jr.*



- ▶ **Chronic Bronchitis in Women Using Solid Biomass Fuel in Rural Peshawar, Pakistan.** *By Dr. T. Akhtar, et al.*
- ▶ **Effective Written Communication for Patients With Limited-English-Proficiency.** *By Dr. T. Oshimi*

Papers Associated With the Global Themes Issue:

- ▶ **Indoor Air Pollution: A Poverty-Related Cause of Mortality Among the Children of the World.** *By Dr. A. Emmelin; and Dr. S. Wall*
- ▶ **Socioeconomic Status and Lung Function.** *By Dr. M. J. Hegewald, FCCP; and R. O. Crapo, FCCP*
- ▶ **Information Technology for Health in Developing Countries.** *By Dr. F. Bukachi; and Dr. N. Pakenham-Walsh*

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Continued from previous page

following questionnaires and a portable, sleep apnea test in the home that demonstrated significant sleep apnea. Dr. Frank Ryan, the senior author of the paper, presented the results of the study to the conferees.

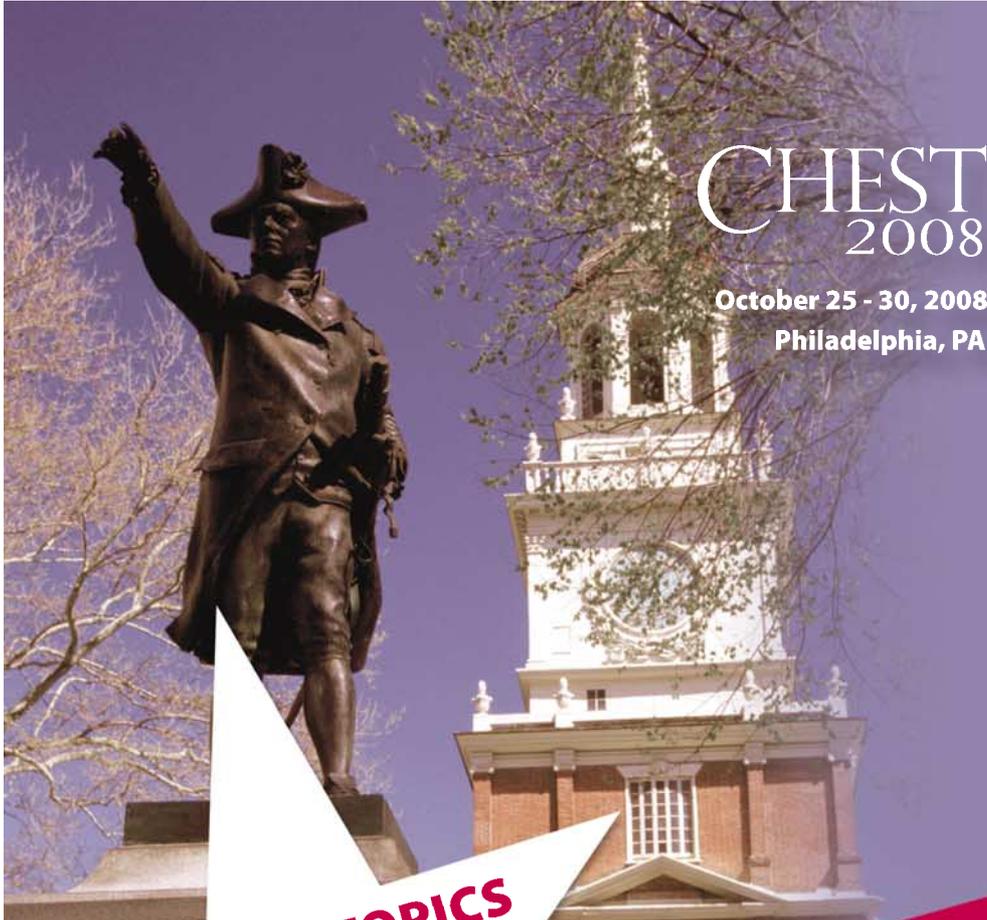
In the end, the voting on the portable monitoring questions was mostly in the middle of the possible range: 3s out of a range of 1 to 5, where higher scores reflect more enthusiasm for portable sleep apnea monitoring.

In my opinion, this gives the Coverage Advisory Group of CMS (the CMS group that recommends changes in coverage decisions) "room to maneuver" when deciding whether to make changes to their current coverage decision about this contentious technology.

CMS plans to announce its coverage decision in December of this year. Some industry watchers believe that the MCAC's lack of a strong "no" vote means that portable monitoring will likely be approved. It may be just as likely that CMS will await the results of two clinical trials, currently underway or being planned in the United States, that will examine clinical outcomes more fully than prior studies.

In either case, portable sleep apnea monitoring is here to stay and will almost certainly remain controversial. ■

*Dr. Charles W. Atwood, Jr., FCCP
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PULMONARY

New York - Position available now or July 1, 2008, for a BC/BE pulmonologist at the Assistant Professor level in the Department of Medicine at Columbia University College of Physicians & Surgeons at The Allen Pavilion, a community hospital of the New York Presbyterian Healthcare Network, staffed by Columbia University. Candidates must be BE/BC in pulmonary medicine. Critical care certification preferred. Primary responsibilities will include clinical practice, academic critical care medicine, and teaching. Opportunity for clinical investigation. Applicants should send (or FAX 212-932-4657) their CV to Joseph Tenenbaum, MD, Chief of Medical Service, The Allen Pavilion, 5141 Broadway, Room 2-272, New York, New York 10034. AA/EOE.

ASSOCIATE DIRECTOR, ICU

Position available now or July 1, 2008. Columbia University, College of Physicians and Surgeons, Department of Medicine, Section of Pulmonary/Allergy/Critical Care Medicine seeks a full-time academic physician at the Assistant Professor level who is BC/BE in critical care medicine. Patient care, teaching rounds, and clinical investigation will be centered in a multidisciplinary ICU at The Allen Pavilion, a community hospital of The New York Presbyterian Healthcare Network, staffed by Columbia University and located at Baker Field in Northern Manhattan. Applicants should send (or FAX 212-932-4657) their CV to Joseph Tenenbaum, MD, Chief of Medical Service, The Allen Pavilion, 5141 Broadway, Room 2-272, New York, New York 10034.

Pulmonary/Critical Care – Richmond, Virginia

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PHYSICIAN RECRUITMENT



Charleston Area
Medical Center

FDA May Call for Label Changes

Cold Meds • from page 1

group. The week before the meeting, however, manufacturers of cough and cold products voluntarily took products with references to infants off the market, and the Consumer Healthcare Products Association (CHPA) and its member companies recommended to the FDA that the "ask a doctor" statement on the labels of these products be changed to "do not use" in children under age 2.

The committees called for industry to conduct efficacy studies in children over age 2, not just pharmacokinetic studies.

Among the other recommendations made by the committees were that statements that a product was "pediatrician recommended," or similar statements on the front panel of these products be eliminated and that all ingredients, with their concentrations and strengths, be listed on the front panel.

The committees also unanimously agreed that clinical studies in children were needed to establish efficacy, with clinical end points that are the symptoms for which the products are marketed.

The ingredients under review are decongestants, first-generation antihistamines, antitussives, and expectorants, which are regulated by a monograph, under which they are classified as "generally recognized as safe and effective," based on advisory committee recommendations from 30 years ago.

After the meeting concluded, Dr. John Jenkins, director of the FDA's office of new drugs, said that because these products are regulated under a monograph, making formal changes to the recommended uses and labeling of these products involves a rule-making process, with a comment period, a laborious process that can take from 1 to several years to finalize.

Therefore, the agency will review the recommendations and comments of the committees, and will issue interim recommendations to the public about the safe and effective use of these products "in the near future," he said.

The recommendations would not necessarily lead to a ban on these products,

but might result in labeling that says they should not be used in children under age 6, for example, Dr. Jenkins said.

The review of these products was prompted by a Citizen Petition filed last year, by Dr. Joshua Sharfstein, a pediatrician and Baltimore City Health Commissioner, with chiefs of pediatric departments at Baltimore medical institutions, which referred to reports of serious injuries and deaths associated with the use of these products in young children.

In the petition, they said that although these products were considered safe by parents and pediatricians, their misuse has been associated with serious adverse effects in children under age 6.

The petition requested that the agency issue a statement to the public that OTC antitussive, expectorant, nasal decongestant, and antihistamine cough and cold products have not been shown to be safe and effective in treating coughs and colds in children under age 6, and that the labeling be changed to state that they should not be used for treating coughs and colds in children under age 6.

The petition also asked the agency to notify manufacturers of these products

that marketing with labels that used terms such as "infant" or "baby" with pictures of children under age 6 is not supported by scientific evidence.

Dr. Sharfstein said at the meeting that while there was no evidence that the products were safe and effective in children aged 6 to under 12, they felt that there was more urgency regarding the use of these products in children younger than 6 years of age.

An FDA review of serious adverse events reported in association with cough and cold products in children younger than age 6 years concluded that the use of these products has been associated with serious adverse events, including deaths in this age group, often related to overdoses that were accidental, intentional, or a result of a medication error. Most involved products that contained multiple ingredients.

After the meeting ended, Dr. Sharfstein said in an interview that "finally, these products were held to a standard of science, and they didn't pass."

A statement issued by CHPA said that the industry would work with the FDA to design "appropriate pediatric clinical efficacy studies." ■

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Asthma Survey Casts Doubt on Hygiene Hypothesis

BY FRAN LOWRY

Elsevier Global Medical News

Preventing common respiratory and gastrointestinal tract illnesses in young children does not make them more prone to develop allergic disorders when they reach their teenage years, Danish researchers reported.

The finding casts doubt on the hygiene hypothesis, first proposed in 1989, which states that a lack of early childhood exposure to infectious agents increases the susceptibility to allergic diseases later in life.

The researchers, led by Dr. Teija Dunder of the University of Oulu (Finland), surveyed a group of adolescents who had participated in a randomized infection prevention trial 12 years earlier.

That trial, also conducted by Dr. Dunder and her colleagues, found that efforts to reduce common infections in child day care centers resulted in 24% fewer prescriptions for antibiotics and 16% fewer days with symptoms of infections among the children randomized to the infection prevention arm.

In this follow-up study, which was undertaken to evaluate the effect of the researchers' success in reducing those infections on the later development of allergic diseases, the rates of asthma, al-



ELSEVIER GLOBAL MEDICAL NEWS

Child using a steroid inhaler. Teens with fewer infections in early childhood were no more likely to develop asthma.

lergic rhinitis, and atopic dermatitis were the same in the group that received the hygiene intervention and the group that did not (Arch. Pediatr. Adolesc. Med. 2007; 161:972-7).

They surveyed 481 teens from the hygiene intervention group, who had markedly fewer infections, and 447 controls. Asthma was diagnosed in 48 teens (10%) in the intervention group and in 46 teens (10%) in the control group.

Also, there were no differences seen in the numbers of teens who had developed

allergic rhinitis or atopic dermatitis as diagnosed by a physician, or who had reported asthma, allergic rhinitis, or atopic dermatitis symptoms, the researchers wrote.

The respondents from both groups were similar with regard to their family history of atopic diseases, duration of breastfeeding, and number of siblings.

The mean ages at which the children were diagnosed with asthma were similar: 4 years in

the intervention group and 4.3 years in the control group. They also were similar at the onset of atopic dermatitis (0.8 years in the intervention group and 0.9 years in the control group) and the onset of seasonal allergic rhinitis (3.8 years in the intervention group and 3.7 years in the control group).

The researchers said that "the magnitude of the reduction in infections and the duration of the intervention in our randomized hygiene intervention trial should have led to an increase in asthma rates if the hygiene hypothesis were to apply to com-

mon childhood infections. ... As our intervention lasted 15 months, we believe that this duration would have been long enough to show at least some effect on the occurrence of asthma, but this was not seen."

They added that in a previous observational study, attendance at day care during the first 6 months of life protected against the development of asthma, as did the presence of one or more older siblings at home (N. Engl. J. Med. 2000;343:538-43). ■

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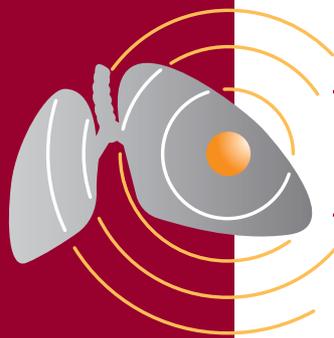
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