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PARKER SMITH/ELSEVIER GLOBAL MEDICAL NEWS

The timing of possible licensure by the FDA may allow PCV13 use during the 2009/2010 flu season, said Dr. Pekka Nuorti.

Panels Move PCV13 Closer to Approval

BY MIRIAM TUCKER & HEIDI SPLETE
Elsevier Global Medical News

ATLANTA & BETHESDA, MD. — A Food and Drug Administration advisory panel has recommended approval of Pfizer's 13-valent pneumococcal conjugate vaccine for the prevention of invasive pneumococcal disease, while a Centers for Disease Control and Prevention advisory panel outlined draft guidelines for its use.

At a meeting last month, the FDA's Vaccines and Related Biological Products Advisory Committee said that the data support efficacy and safety of Prevnar 13, based on two phase III trials involving a total of 2,362 subjects randomized to either PCV13 or PCV7 at 2, 4, 6, and 12-15 months of age.

If it is approved for use in the United States, a 13-valent pneumococcal conjugate vaccine in children would have recommendations mirroring those already in place for the 7-valent vaccine. At an earlier meeting in October, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices presented draft guidelines for PCV13 use.

The 13-valent formulation is composed of capsular polysaccharides derived from the seven pneumococcal serotypes contained in the current 7-valent Prevnar (4, 6B, 9V, 14, 18C, 19F, and 23F), and from six additional serotypes (1, 3, 5, 6A, 7F, and 19A). It is manufactured in the same way as Prevnar, by individual conjugation of each capsular polysaccharide to diphtheria protein, said Dr. Emilio A. Emini, Pfizer Inc.'s chief scientific officer for vaccine research.

At the time PCV7 was licensed in 2000, its seven strains accounted for 80% of invasive pneumococcal disease (IPD) in young children in North America, according to Dr. Matthew R. Moore, an epidemiologist at the CDC. Although the rates of IPD from PCV7 strains then declined by 99%, overall IPD rates began

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Probiotic Helped Prevent VAP, *C. difficile* Disease

Antibiotic use also lower in ICU.

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Giving the probiotic Lactobacillus GG to critically ill patients on mechanical ventilation resulted in markedly reduced rates of ventilator-associated pneumonia and *Clostridium difficile* disease in a double-blind, placebo-controlled study.

"Probiotic therapy looks like it may provide us with a novel, inexpensive, and—most importantly—nonantibiotic opportunity for prevention of VAP [ventilator-associated pneumonia]. It may also provide us with an opportunity to prevent other nosocomial infections," Dr. Lee E. Morrow, FCCP, said at CHEST 2009, the annual meeting of the American College of Chest Physicians.

He reported on 138 patients admitted to a tertiary center ICU with an anticipated need for more than 72 hours of mechanical ventilation, placing them at high risk for VAP. Participants were stratified on the basis of APACHE II scores, and randomized to double-blind administration of 10^9 CFU of the commercially available probiotic Lactobacillus GG (68 patients) or placebo (70 patients) every 12 hours. The first daily dose was delivered in a slurry to the oropharynx, the second in sterile water via nasogastric tube to the stomach.

The primary end point was the incidence of microbiologically confirmed VAP, which was 19% in the probiotic group and 40% in the control patients, a significant difference, according to Dr. Morrow of Creighton University, Omaha, Neb.

The rate of clinically diagnosed VAP using the American

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INSIDE

Guideline Revised for Stage IV NSCLC

BY BETSY BATES
Elsevier Global Medical News

The first substantial revisions in the American Society of Clinical Oncology's clinical guideline for the treatment of stage IV non-small cell lung cancer in 6 years acknowledges the burgeoning role for individualization of therapy according to patient characteristics, including epidermal growth factor receptor mutation status and performance status rather than age.

The guideline, which compiles evidence from 190 scientific papers published since 2002, was published online Nov. 16 in the Journal of Clinical Oncology (DOI: 10.1200/JCO.2009.23.5622).

The current guideline does not advocate customizing therapeutic choices based on molecular marker analysis beyond epidermal growth factor receptor (EGFR) typing as routine practice, although the authors urged future research that could "build on these discoveries" to tailor

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Pneumococcal Vaccine Reviewed

PCV13 • *from page 1*

to level off in 2002, because of an increase in the incidence of IPD caused by non-PCV7 strains, particularly 19A.

The six additional pneumococcal strains contained in PCV13 were responsible for approximately 62% of IPD cases in children younger than 5 years of age in 2007. In the same age group, the 13 serotypes contained in PCV13 were responsible for approximately 64% of IPD cases in 2007, Dr. Moore said.

At the FDA advisory panel meeting, some members questioned whether the data support an indication for PCV13 for prevention of otitis media, which was included in Pfizer's licensing application. The committee didn't vote on that issue, but several members requested further otitis media data for the six additional strains contained in PCV13 that were not in the current 7-valent Prevnar.

The timing of possible licensure by the FDA may allow for use of PCV13 during the 2009/2010 flu season, noted Dr. Pekka Nuorti of the CDC, who presented the draft recommendations at ACIP's October meeting. ACIP member Dr. Michael Marcy cited recent data from the CDC's Morbidity and Mortality Weekly Report that showed a significant association between bacterial coinfections and severe cases of the pandemic influenza A (H1N1) virus.

To expedite a potential transition to PCV13, the CDC said provisions are in place for voting on vaccine recommendations in advance of the next scheduled ACIP meeting in February, noted Dr. Melinda Wharton, acting director of the CDC's National Center for Immunization and Respiratory Diseases.

ACIP Outlines PCV13 Guidelines

ACIP's draft recommendations involve four groups: unvaccinated infants and children, children who have started their PCV vaccine schedules with PCV7, children who have completed the PCV7 schedule, and immunocompromised children or children with chronic illness.

For unvaccinated infants and children, the recommendations are the same as for PCV7, with PCV13 replacing PCV 7 for all doses, said Dr. Nuorti.

The draft recommendations also state that children who began their vaccination series with PCV7 can complete the series with PCV13 at any point in the schedule, and children who have completed the primary infant series with PCV7 should receive a single PCV13 dose during the second year of life to provide protection against the six additional serotypes.

In addition, the draft recommendations propose a fifth "catch-up" dose for all children aged 12 through 59 months who have received all four PCV7 doses. The catch-up dose will provide protection against the six additional serotypes, Dr. Nuorti said.

Dr. Nuorti added that the proposed recommendations for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) after PCV13 for individuals aged 2 years and older with underlying medical conditions are the same as those currently recommended for the use of PPSV23 after PCV7, although no safety and immunogenicity data are yet available for this vaccine sequence.

Dr. Peter Paradiso of Wyeth Pharmaceuticals presented safety and immunogenicity data. The studies suggest that the safety profiles and immune responses were similar to those seen with PCV7. Both Pfizer and the FDA announced plans to conduct phase IV postmarketing studies of efficacy and safety. ■

Dr. Burt Lesnick, FCCP, comments: *Pneumococcal vaccination rates are often low in those patients most at risk for bacterial pneumonias. This will likely become an important quality measure in the near future. The additional option of a 13-valent vaccine broadens coverage for young children, while the 23-valent vaccine remains the standard for those older than 24 months.*

IN THIS ISSUE

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Prophylaxis Shows Promise

Probiotic • *from page 1*

College of Chest Physicians (ACCP) criteria was 25% in the probiotic group, compared with 47% with placebo. The ACCP criteria consist of a new infiltrate on chest x-ray plus any two of the following three clinical criteria: fever, purulent sputum, or leukocytosis.

The incidence of *C. difficile* disease as diagnosed by cytotoxic assay was 6% in the probiotic group and 19% in controls. The duration of ICU-associated diarrhea also was significantly lower in the probiotic group: a mean of 3.1 days, compared with 6.2 days in controls.

Patients who received the probiotic received antibiotics for pneumonia for a mean of 5.6 days, significantly less than the 8.6 days in controls. They received antibiotics specifically for *C. difficile* infection for a mean of 0.5 days, compared with 2.1 days in controls.

Hospital charges averaged $66,000 more per patient in the placebo arm because of their longer ICU and overall hospital lengths of stay, along with their additional need for expensive antibiotics. Hospital cost data weren't available.

Several secondary end points showed intriguingly consistent trends, albeit statistically nonsignificant, in favor of probiotic prophylaxis. For example, the probiotic group had a 12% hospital mortality rate, compared with 17% in controls. They also had a 38% incidence of bacteremia and a 21% urinary tract infection rate, compared with rates of 73% and 33%, respectively, with placebo. Probiotic prophylaxis had no side effects.

Serial cultures using oral swabs and gastric aspirates showed a clear trend toward preservation of a normal mixed upper respiratory flora in the probiotic group, with less appearance of potentially pathogenic species than in controls.

The probiotic treatment concept adopts measures to modify the gut flora in order to replace harmful microbes with useful ones. The mechanisms of benefit aren't fully understood, but immunomodulation appears to figure prominently. Ligands on the commensal organisms interact with toll-like receptors on gut-associated lymphatic tissue, which releases signals promoting immune system homeostasis, Dr. Morrow explained.

Dr. Morrow disclosed that the probiotic study was funded entirely by noncommercial entities, including the National Institutes of Health and the American College of Chest Physicians. The next logical step, he said, would be a large multicenter trial powered to show whether the favorable mortality trend observed in the Omaha trial is real. ■

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Panel Supports Spiriva to Reduce COPD Exacerbations

Inhaled tiotropium reduced number of COPD exacerbations, FDA advisory panel finds.

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

SILVER SPRING, MD. — A Food and Drug Administration advisory panel on Nov. 19 voted 11 to 1 that evidence from two studies was sufficient to support approval of a claim that treatment with the inhaled, dry-powder formulation of tiotropium reduces exacerbations in patients with chronic obstructive pulmonary disease.

At the meeting, 11 of the 12 members of the FDA's Pulmonary-Allergy Drugs Advisory Committee also voted that data from one of those studies, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, "adequately addressed" the potential safety signals of an increased risk of stroke and adverse cardiovascular outcomes associated with this product that have been recently identified in pooled data and meta-analyses of tiotropium studies.

The dry-powder formulation of tiotropium is marketed as the Spiriva HandiHaler by Boehringer Ingelheim and Pfizer. This medication was approved in the United States in January 2004 for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disorder (COPD), including chronic bronchitis and emphysema. It is administered once daily; each inhalation contains a dose of 18 mcg of tiotropium, an anticholinergic.

The companies proposed that Spiriva be approved for reductions in COPD exacerbations based on the UPLIFT trial and the Veterans Affairs (VA) Exacerbations Trial.

In the 6-month VA study, there were approximately 1,800 patients with COPD, most of whom were men and whose mean age was 68 years. The two primary end points—the proportion of patients with COPD exacerbations and the proportion of patients hospitalized for exacerbations—were significantly lower among those on Spiriva than in those on placebo: 27.9% of those on Spiriva and 32.3% of those on placebo had at least one exacerbation during the study, a significant difference (P value 0.037), and 7% of those on Spiriva had at least one exacerbation requiring hospitalization, compared with 9.5% of those on placebo, which approached significance ($P = .056$).

IN A 6-MONTH VA STUDY, 27.9% OF PATIENTS ON SPIRIVA HAD AT LEAST ONE EXACERBATION, VS. 32.3% OF THOSE ON PLACEBO.

The median time to the first exacerbation and to the first exacerbation resulting in hospitalization, secondary end points, were also reduced among those on Spiriva, compared with those on placebo.

In the UPLIFT study, a multinational, randomized, placebo-controlled, 4-year study comparing tiotropium to placebo in almost 3,000 COPD patients, the number of COPD exacerbations, which was a secondary end point, was significantly lower among those on Spiriva over 4 years than among those on placebo.

Also in the UPLIFT study, the risks for stroke, cardiovascular events, and mortality were all lower among those on Spiriva when compared with placebo. The FDA's analysis concluded that the UPLIFT data did not suggest an increased risk for stroke or cardiovascular events, and suggested that the data supported a decrease in mortality associated with treatment. (The risk of mortality was reduced by 27% in this study.)

The FDA usually follows the recommendations of its advisory panels. Another treatment approved for COPD, the combination of fluticasone propionate and salmeterol inhalation powder marketed as Advair Diskus, has been approved for reducing COPD exacerbations. ■

INLIGHT 2 Trial: Indacaterol Topped Salmeterol for COPD

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — The investigational ultralong-acting inhaled $beta_2$-agonist indacaterol outperformed salmeterol and placebo in a double-blind, randomized clinical trial involving 998 patients with moderate to severe COPD.

Once-daily indacaterol provided sustained bronchodilation throughout the 24-hour day at 12 and 26 weeks that was superior to that of twice-daily salmeterol (Serevent) or placebo.

Moreover, indacaterol-treated patients experienced significantly less dyspnea and need for rescue medication and greater improvement in health status than patients in the other two study arms, Dr. Oliver Kornmann reported at CHEST 2009, the annual meeting of the American College of Chest Physicians.

AT WEEK 12, 60% OF THE INDACATEROL PATIENTS HAD A MEANINGFUL REDUCTION IN DYSPNEA, VS. 51% OF THE SALMETEROL GROUP.

The results of INLIGHT 2 (Indacaterol: Efficacy Evaluation Using 150 Mcg-Doses With COPD Patients–2) indicate that indacaterol administered via single-dose dry powder inhaler will be an attractive option for maintenance therapy in patients with moderate-to-severe COPD, according to Dr. Kornmann, a pulmonologist at Mainz (Germany) University Hospital.

The primary study end point was trough forced expiratory volume in 1 second (FEV_1) at week 12, which was 60 mL greater with indacaterol than salmeterol and 170 mL more than with placebo. Although these differences were statistically significant, the prespecified definition of clinical significance was a 120 mL difference, he noted.

A key secondary end point was health status as assessed using the St. George's Respiratory Questionnaire. At week 12, the total score in the indacaterol group was improved over baseline by 6.3 points more than placebo and 2.1 points more than salmeterol, which was dosed at 50 mcg twice daily using its proprietary dry powder inhaler. A total of 58% of indacaterol-treated patients achieved at least a 4-point improvement, as did 47% on salmeterol and 39% on placebo.

The odds of achieving a clinically meaningful improvement in health status by this measure with indacaterol therapy were 1.6-fold greater than with salmeterol and 2.4-fold greater than with placebo.

The indacaterol group didn't require rescue albuterol on 60% of days over the course of 26 weeks of follow-up. That was significantly better than the 55% rate with salmeterol and 42% with placebo.

At week 12, 60% of indacaterol-treated patients had achieved a clinically meaningful reduction in dyspnea as defined by at least a 1-point improvement in Transition Dyspnea Index total score, as did 51% of the salmeterol group and 40% on placebo. All these differences were significant.

Serious adverse events occurred in 8.8% of patients on indacaterol, 5.7% on salmeterol, and 7.8% on placebo.

A total of 18% of the indacaterol group experienced worsening of COPD, as did 15% on salmeterol and 19% on placebo, although most exacerbations were mild to moderate.

Of note, prolongation of the QT interval on ECG in excess of 450 milliseconds for men and 470 milliseconds for women occurred in 5.2% of the indacaterol group, 1.8% of the salmeterol group, and 3.3% with placebo.

Bacterial or viral upper respiratory infections occurred in 7.2% of the indacaterol group, 1.8% of salmeterol-treated patients, and 3.6% on placebo.

INLIGHT 2 participants averaged 63 years of age and had to have a smoking history of 20 pack-years or more.

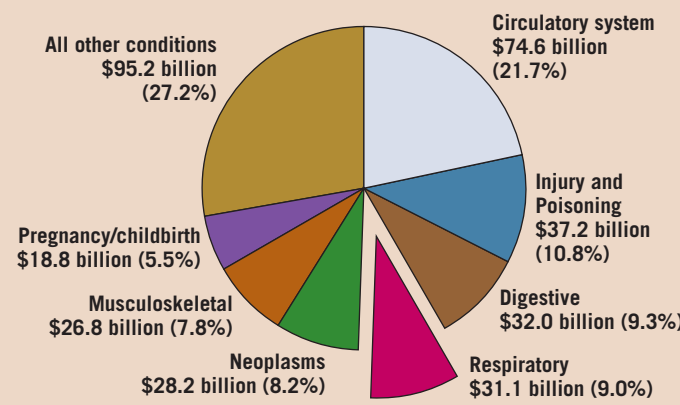
The study was sponsored by Novartis. Dr. Kornmann is a consultant to the company.

Indacaterol has been endorsed for marketing approval by the European Committee for Medicinal Products. In contrast, the FDA has deemed the application for U.S. licensure not approvable at present and has requested additional data from Novartis. ■

Dr. Philip Marcus, MPH, FCCP, comments: *The management of COPD includes the use of bronchodilators beginning at step 2, which recommends the use of one or more long-acting bronchodilators. Thus far, only tiotropium, a long-acting anticholinergic, is available for once-daily use. The studies on indacaterol, an "ultra-long-acting" $beta_2$-agonist, suggest that it could also be used once daily in the treatment of moderate to very severe COPD. The safety profile appears acceptable, and we await further studies with this compound.*

DATA WATCH

Respiratory Conditions Accounted for 9% of Hospital Costs in 2007



Note: Based on data from the Healthcare Cost and Utilization Project.
Source: Agency for Healthcare Research and Quality

ELSEVIER GLOBAL MEDICAL NEWS

Roflumilast Improved Lung Function in COPD

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Roflumilast improved lung function and prevented exacerbations in patients with COPD with chronic bronchitis and severe airflow obstruction in a 12-month randomized trial.

Results of the 1,568-patient, double-blind, placebo-controlled study known as the M2-125 trial indicate roflumilast is an important potential new advance in the treatment of a subset of patients with COPD, Dr. Andrew McIvor, FCCP, declared at CHEST 2009, the annual meeting of the American College of Chest Physicians.

Roflumilast (Daxas) is an investigational selective phosphodiesterase 4 inhibitor, a drug class that represents a novel approach to the treatment of COPD. Taken orally once daily, roflumilast targets the inflammation that's a hallmark of the disease, explained Dr. McIvor of St. Joseph's Healthcare Hamilton, Ont.

Participants in the eight-nation M2-125 trial had to have at least one documented moderate or severe COPD exacerbation during the year prior to enrollment. They were randomized to roflumilast 500 mcg once daily or placebo for 1 year, on top of background long-acting beta$_2$-agonist or short-acting anticholinergic therapy at stable doses, along with short-acting beta$_2$-agonists as needed. Long-acting anticholinergics and inhaled corticosteroids were not permitted.

The rate of moderate to severe COPD exacerbations requiring systemic steroids and/or treatment in a hospital—one of two co-primary study end points—was 1.21 cases per patient per year in the roflumilast group and 1.49 in controls, for a highly significant 18.5% relative risk reduction.

The other primary end point was improvement in lung function as reflected in mean change from baseline in forced expiratory volume in 1 second (FEV_1) prior to administration of a bronchodilator. Again, roflumilast showed a highly significant advantage, with a 33-mL increase in FEV_1 as compared to a 25-mL decrease with placebo over the course of a 12-month period.

The change in postbronchodilator FEV_1 over time—a secondary end point—consisted of a 44-mL increase with roflumilast as compared to a 17-mL decrease with placebo, also a significant difference.

THE RATE OF MODERATE TO SEVERE COPD EXACERBATIONS WAS 1.21 CASES PER PATIENT PER YEAR IN THE ROFLUMILAST GROUP AND 1.49 IN CONTROLS.

The other prespecified secondary end point was time to death from any cause, which was similar in the two study arms at 201 days for roflumilast and 215 days for placebo. All-cause mortality was 3% per year in each of the groups.

Adverse events were mostly mild in nature. The two that were more frequent in the roflumilast arm were diarrhea and weight loss, affecting 9% and 8% of patients, respectively.

In addition to the sort of patients enrolled in M2-125, the other subset of COPD patients in which roflumilast has shown compelling efficacy in large trials is those with moderate to severe COPD who are on long-acting bronchodilators, according to Dr. McIvor.

The M2-125 study was sponsored by Nycomed, formerly Altana Pharma. Dr. McIvor is a consultant to the company. ■

Dr. Philip Marcus, MPH, FCCP, comments: *The management of COPD continues to evolve. The expected introduction of roflumilast, and probably other drugs in this class, should improve outcomes for many patients who remain symptomatic despite conventional therapies, including long-acting beta agonists, long-acting anticholinergics, and inhaled corticosteroids.*

This study, like other recently published studies with this agent, has shown the ability to reduce exacerbations and improve pulmonary function in patients currently treated with other options. Where this will fit in the guideline approach to COPD management remains to be determined as more studies are undertaken.

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FDA Panel Backs Thermoplasty Device for Asthma

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

GAITHERSBURG, MD. — A Food and Drug Administration advisory panel voted 6 to 1 that a novel device that uses thermal energy to ablate smooth muscle in the airway during bronchoscopy could be approved under certain conditions as a treatment for severe, persistent asthma in people aged 18 years and older.

At the October meeting, members of the FDA's Anesthesiology and Respiratory Therapy Devices Panel agreed that there was reasonable evidence that the device was safe and effective for this indication, but stipulated several conditions for approval, reflecting concerns about the need for longer-term safety and efficacy data.

In the United States, 22 million people have asthma; 5%-10% of those people have severe asthma, according to the FDA.

The conditions included requiring the manufacturer to enroll all patients treated with the device after approval in a registry, which would follow the durability of the therapeutic effects and safety; and not using the device in patients with impaired coagulation or on those who are on anticoagulant medication, because hemoptysis was reported in six treated patients in the pivotal study.

Other conditions for approval were that physicians who use the device be adequately trained, and that patients not be retreated with the device until clinical trial data on the effects of retreatment are available.

The panel also unanimously recommended postmarketing studies to further evaluate the safety and effectiveness of the device, with end points that include emergency department visits for respiratory symptoms, corticosteroid requirements, asthma exacerbations, and hospitalizations.

Components of the Alair Bronchial Thermoplasty system include a radiofrequency generator and a single-use catheter with an electrode basket at the tip that delivers radiofrequency (RF) energy to surrounding tissue.

Treatment results in clinical improvements in people with severe asthma by using thermal energy "to reduce the airway smooth muscle responsible for airway constriction in asthma patients," according to the device's manufacturer, Asthmatx.

THE DEVICE USES THERMAL ENERGY TO REDUCE THE SMOOTH MUSCLE RESPONSIBLE FOR AIRWAY CONSTRICTION IN ASTHMA PATIENTS.

The pivotal study conducted in six countries compared treatment with the device in 190 patients to sham bronchoscopy in 98 patients (where the catheter was deployed, without RF). Patients, whose median age was 41 years, had severe persistent asthma that was "not well controlled" (30%) or "very poorly controlled" (70%), and required high doses of inhaled corticosteroids and long-acting beta agonist therapy. Treatment was administered during three separate outpatient bronchoscopies 3 weeks apart. Each procedure took about 30 minutes, according to Asthmatk.

The primary end point was the average of the changes in 6, 9, and 12 month Asthma Quality of Life Questionnaire (AQLQ) scores, a patient self-administered validated questionnaire, from baseline. Scores increased among patients in both groups, but the average of the three scores was 0.21 points greater among those in the active treatment group, compared with those in the sham group, which just missed statistical significance, according to the FDA's analysis.

The largest effects of treatment were seen at U.S. study sites. In Brazil, however, improvements in the scores were somewhat higher among those in the sham group, which panelists agreed was a concern. Some panelists thought that may have been due to the free maintenance medications received by all the patients enrolled at the Brazil sites, possibly reflecting greater compliance with medication therapy.

Some of the study's secondary end points, including rates of severe exacerbations after treatment; days lost from work, school, or other daily activities due to asthma symptoms; and emergency department visits for respiratory symptoms, were lower among those treated with the device. Nearly 79% of those on Alair had a change in the AQLQ score of at least 0.5 (which the company said is the threshold for a clinically meaningful change), compared with 64.3% of those on sham treatment, the company reported.

Respiratory-related events, including asthma symptoms, were higher among those in the device-treated patients during the treatment phase (from the time of the first bronchoscopy through 6 weeks after the third bronchoscopy) but lower than among those in the sham group after that time. A total of 6 patients (3%) treated with the device had hemoptysis, which typically occurred soon after the procedure and was self-limited; one patient developed severe hemoptysis 31 days after treatment. But there were no cases in sham-treated patients. There were no treatment-related deaths or withdrawals for worsening asthma in the study.

Although the primary effectiveness end point in the pivotal study was not met, panelists supporting approval said they considered some of the secondary end points clinically relevant.

The panel generally agreed that the device appeared to be safe, but that long-term safety should be monitored, including the potential for dysplastic changes and malignancy in the treated areas. (There has been no evidence of structural abnormalities or neoplasia during up to 5 years of follow-up, according to Asthmatx.)

Panelist Dr. Sharon Rounds said that, despite her concerns about the regional variability in the effectiveness results, she was impressed with the secondary end points. "On balance, the risks are offset by the reasonably effective nature of the intervention," noted Dr. Rounds, chief of pulmonary/critical care at Providence VA Medical Center, Providence, R.I.

A long-term study following patients for at least 5 years after treatment is needed, however, to monitor treatment durability and potential long-term sequelae of "undoubted damage to the epithelium and other components of the airway wall, in addition to bronchial smooth muscle," she cautioned.

The FDA usually follows the recommendations of its advisory panels. If approved, Asthmatx plans further studies, including one that will follow patients in the pivotal trial through 5 years. The company also will provide didactic and interative training for physicians. ■

Dr. Philip Marcus, MPH, FCCP, comments: *The management of patients with severe asthma, a group of patients generally felt to be difficult to treat, has evolved with the last update of the NAEPP guidelines. However, despite optimal therapy with essentially all available agents, a subgroup of patients exists for whom other options are needed. The use of this novel, nonpharmacologic therapy may be what we have been looking for. However, caution is needed until the technique is studied more to exactly define the group of patients who might benefit.*

FDA Panel Says No to Expanded Indication for Omalizumab

BY ELIZABETH MECHCATIE
Elsevier Global Medical News

SILVER SPRING, MD. — The majority of a Food and Drug Administration advisory panel did not support expanding the approval of omalizumab as a treatment for moderate to severe persistent asthma to include children aged 6-11 years, based on available safety and efficacy data.

The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 10-4 that the safety and efficacy data on omalizumab did not provide "substantial and convincing evidence" to support approval for the proposed indication: the treatment of asthma in patients aged 6-11 years with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICS) and who have a positive skin test or in vitro reactivity to a perennial aeroallergen. Omalizumab, a monoclonal antibody that reduces serum IgE levels, was approved in 2003 for the same indication in adolescents and adults aged 12 years and older.

It is marketed as Xolair by Genentech USA Inc. and Novartis Pharmaceuticals.

A marginal effect on efficacy and outstanding safety issues, including concerns about long-term safety, anaphylaxis risk, and unknown implications of circulating levels of omalizumab-IgE immune complexes in some treated patients, were among the reasons panelists said they voted against approval.

Omalizumab is administered subcutaneously, every 2-4 weeks in a health care setting, at a dose based on serum IgE levels and body weight. The current label has warnings about the potential risks of anaphylaxis and malignancies associated with treatment, based on clinical trial data and postmarketing reports. In July 2009, the FDA reported that a cardiovascular safety signal associated with omalizumab was identified in postmarketing reports.

Omalizumab was evaluated in a pivotal 52-week study of 627 children aged 6-11 years with moderate to severe persistent, inadequately controlled allergic asthma, despite treatment with fluticasone at dose of 200 mcg or more per day (or the equivalent), with or without other controller medications, which included short-acting beta-agonists (a mean of 2.8 puffs/day) and leukotriene antagonists (37%). The primary end point, the rate of clinically significant asthma exacerbations (defined as worsening of symptoms requiring a doubling of the baseline ICS dose for 3 days or more and/or treatment with rescue systemic IV or oral steroids for 3 days) at 24 weeks, was 0.45 in those treated with omalizumab, versus 0.64 in those on placebo, a significant difference.

One secondary efficacy end point, the asthma exacerbation rate at 52 weeks, was significant in favor of omalizumab (0.78 among those on omalizumab, versus 1.30 among those on placebo). The other secondary end points—nocturnal symptom scores, asthma medication rescue use, and quality of life scores at 24 weeks—were not significantly different between the two groups.

The most common adverse effects in pediatric studies were nasopharyngitis, upper respiratory tract infections, and headache; these were reported at similar rates in those on placebo and omalizumab. No new safety signals were identified, and there were no malignancies among omalizumab-treated patients. The one case of anaphylaxis in an omalizumab-treated patient was associated with a meperidine hydrochloride (Demerol) injection.

The FDA usually follows the recommendations of its advisory panels. ■


temp: 101.9F
O2 sat: 89%
WBC: 18.1
MRSA
nosocomial pneumonia
PMNs: 80%, bands: 15%
creatinine: 2.6
CXR: LLL infiltrate

Some patients have ZYVOX written all over them

With proven efficacy, excellent tissue penetration, and clear and consistent dosing, count on ZYVOX to treat MRSA* in patients with nosocomial pneumonia whose conditions are complicated by renal insufficiency.[1-3]

IV/Oral
ZYVOX®
(linezolid)

CONFIDENCE TO FACE COMPLEXITY

ZYVOX is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers.

ZYVOX use is contraindicated in patients with known hypersensitivity to linezolid or any of the other product components.

ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such product.

Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following: directly and indirectly acting sympathomimetic, vasopressive, and dopaminergic agents.

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists, meperidine, or buspirone.

Spontaneous reports of serotonin syndrome have been reported with the coadministration of ZYVOX and serotonergic agents. If signs or symptoms of serotonin syndrome, such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination occur, discontinuation of one or both agents should be considered.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters returned to pretreatment levels. Complete blood counts should be monitored weekly, particularly in patients who receive ZYVOX for longer than 2 weeks.

ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis.

Lactic acidosis has been reported with the use of ZYVOX. Patients receiving ZYVOX who develop recurrent nausea, vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation.

Peripheral and optic neuropathy have been reported primarily in patients treated with ZYVOX for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, prompt ophthalmic evaluation is recommended.

Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported.

The most commonly reported adverse events in adults across phase 3 clinical trials were diarrhea, nausea, and headache.

*Methicillin-resistant *Staphylococcus aureus*.

References: 1. Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG; and Linezolid Nosocomial Pneumonia Study Group. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. *Clin Infect Dis*. 2001;32(3):402-412. **2.** Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH; for Linezolid Nosocomial Pneumonia Study Group. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*. 2003;25(3):980-992. **3.** Boselli E, Breilh D, Rimmelé T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med*. 2005;33(7):1529-1533.

Please see brief summary on adjacent pages.

ASCO Updates Guideline

NSCLC • *from page 1*

treatment options according to which patients might benefit most.

"While research on NSCLC molecular markers is constantly changing, the guideline has to reflect the current state of published literature," Dr. Guiseppe Giaccone, co-chair of the American Society of Clinical Oncology (ASCO) guideline committee and head of the thoracic oncology section branch of the National Cancer Institute, said in an interview.

"This posed a challenge [in developing the guideline], because the gold standard for the use of markers is that they must show that their use prolongs overall survival, and the current evidence does not show that," he said.

The new guideline recommends combination chemotherapy as the first-line treatment in most patients, with either cisplatin or carboplatin deemed acceptable as the first drug in the combination.

Third-generation cytotoxic drugs affirmed as acceptable in combination with cisplatin or carboplatin include docetaxel (Taxotere), gemcitabine (Gemzar), irinotecan (Camptosar), paclitaxel (Taxol), pemetrexed (Alimta), and vinorelbine (Navelbine).

Previous ASCO guidelines failed to address how the decision should be made to start with cisplatin or carboplatin, the committee noted.

"The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin, but is more likely to cause thrombocytopenia," according to the new guideline.

Recommendations for the duration of first-line therapy were also revised, based on modern trial data. However, the recent approval of a maintenance indication for pemetrexed may require an update, Dr. Giaccone said in an interview.

"Due to the timing of this publication, ASCO will have to re-examine the recommendation not to continue cytotoxic

ZYVOX® linezolid injection, tablets and for oral suspension
Brief summary of prescribing information.

INDICATIONS AND USAGE ZYVOX formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms **(see PRECAUTIONS, Pediatric Use). Vancomycin-Resistant *Enterococcus faecium* infections**, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]). **Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis**, caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. ZYVOX has not been studied in the treatment of decubitus ulcers. **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible only) or *Streptococcus pyogenes*. **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP*]), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZYVOX and other antibacterial drugs, ZYVOX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS ZYVOX formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. ZYVOX should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, ZYVOX should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), and dopaminergic agents (e.g. dopamine, dobutamine). Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone.

WARNINGS Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving ZYVOX. In cases where the outcome is known, when ZYVOX was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive ZYVOX, particularly in those who receive ZYVOX for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with ZYVOX should be considered in patients who develop or have worsening myelosuppression. In adult and juvenile dogs and rats, myelosuppression, reduced extramedullary hematopoiesis in spleen and liver, and lymphoid depletion of thymus, lymph nodes, and spleen were observed. **Mortality Imbalance in an Investigational Study in Patients With Catheter-related Bloodstream Infections, Including Those With Catheter-site Infections.** ZYVOX is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. In an open-label investigational study in seriously ill patients with intravascular catheter-related infections, an imbalance in mortality was seen in patients treated with ZYVOX compared with vancomycin/dicloxacillin/oxacillin. While causality has not been established, mortality was higher in patients treated with ZYVOX who were infected with Gram-negative organisms alone, with both Gram-positive and Gram-negative organisms, or who had no infection when they entered the study. Patients with Gram-positive infections had no difference in mortality. ZYVOX has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. *Clostridium difficile*–associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including ZYVOX, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C difficile*. *C difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS General Lactic acidosis has been reported with the use of ZYVOX. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ZYVOX should receive immediate medical evaluation. Spontaneous reports of serotonin syndrome associated with the co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see PRECAUTIONS, Drug Interactions). Where administration of ZYVOX and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms). Peripheral and optic neuropathy have been reported in patients treated with ZYVOX, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with ZYVOX for less than 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ZYVOX for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOX.** If peripheral or optic neuropathy occurs, the continued use of ZYVOX in these patients should be weighed against the potential risks. Convulsions have been reported in patients treated with ZYVOX. In some of these cases, a history of seizures or risk factors for seizures was reported. The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. ZYVOX has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. The safety and efficacy of ZYVOX formulations given for longer than 28 days have not been evaluated in controlled clinical trials. Prescribing ZYVOX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Information for Patients** Patients should be advised that: ZYVOX may be taken with or without food. They should inform their physician if they have a history of hypertension. Large quantities of foods or beverages with high tyramine content should be avoided while taking ZYVOX. Quantities of tyramine consumed should be less than 100 mg per meal. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses (0 to 15 mg tyramine per ounce); fermented or air-dried meats (0.1 to 8 mg tyramine per ounce); sauerkraut (8 mg tyramine per 8 ounces); soy sauce (5 mg tyramine per 1 teaspoon); tap beers (4 mg tyramine per 12 ounces); red wines (0 to 6 mg tyramine per 8 ounces). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated. They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants. They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants. *Phenylketonurics:* Each 5 mL of the 100 mg/5 mL ZYVOX for Oral Suspension contains 20 mg phenylalanine. The other ZYVOX formulations do not contain phenylalanine. Contact your physician or pharmacist. They should inform their physician if they experience changes in vision. They should inform their physician if they have a history of seizures. Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible. Patients should be counseled that antibacterial drugs including ZYVOX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZYVOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZYVOX or other antibacterial drugs in the future. **Drug Interactions *Monoamine Oxidase Inhibition:*** Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents. *Adrenergic Agents:* Some individuals receiving ZYVOX may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response. *Serotonergic Agents:* Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in Phase 1, 2 or 3 studies. Spontaneous reports of serotonin syndrome associated with co-administration of ZYVOX and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with ZYVOX and concomitant serotonergic agents should be closely observed as described in the PRECAUTIONS, General Section. **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions. **Pregnancy Teratogenic Effects. Pregnancy Category C:** Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.5-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen (see **Non-teratogenic Effects**). There are no adequate and well-controlled studies in pregnant women. ZYVOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Non-teratogenic Effects** In mice, embryo and fetal toxicities were seen only at doses that caused maternal toxicity (clinical signs and reduced body weight gain). A dose of 450 mg/kg/day (6.5-fold the estimated human exposure level based on AUCs) correlated with increased postimplantational embryo death, including total litter loss, decreased fetal body weights, and an increased incidence of costal cartilage fusion. In rats, mild fetal toxicity was observed at 15 and 50 mg/kg/day (exposure levels 0.22-fold to approximately equivalent to the estimated human exposure, respectively based on AUCs). The effects consisted of decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. Slight maternal toxicity, in the form of reduced body weight gain, was seen at 50 mg/kg/day. In rabbits, reduced fetal body weight occured only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) when administered at a dose of 15 mg/kg/day (0.5-fold the estimated human exposure based on AUCs). When female rats were treated with 50 mg/kg/day (approximately equivalent to the estimated human exposure based on AUCs) of linezolid during pregnancy and lactation, survival of pups was decreased on postnatal days 1 to 4. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss. **Nursing Mothers** Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZYVOX is administered to a nursing woman. **Pediatric Use** The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infections are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from a comparator-controlled study of Gram-positive infections in pediatric patients ranging in age from birth through 11 years (see **INDICATIONS AND USAGE**): nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia (also supported by evidence from an uncontrolled study in patients ranging in age from 8 months through 12 years), vancomycin-resistant *Enterococcus faecium* infections. The safety and effectiveness of ZYVOX for the treatment of pediatric patients with the following infection have been established in a comparator-controlled study in pediatric patients ranging in age from 5 through 17 years: uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*. Pharmacokinetic information generated in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended. The C_{max} and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, linezolid clearance is a function of age. Excluding neonates less than a week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence, mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and in systemic drug exposure (AUC) across all pediatric age groups as compared with adults. Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed q8h relative to adolescents or adults dosed q12h. Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h. Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC

chemotherapy beyond specified limits or initiate different chemotherapy prior to disease progression," he explained.

The 2009 guideline suggests that first-line cytotoxic chemotherapy should be discontinued at disease progression or after 4 cycles in patients who are not responding.

Further, the guideline calls for stopping a two-drug cytotoxic regimen after 6 cycles, even in responders and patients with stable disease.

For the first time, the ASCO guideline advocates consideration of agents based on EGFR status, with cetuximab (Erbitux) a possibly advantageous adjunct to cisplatin plus vinorelbine in first-line therapy, and gefitinib (Iressa) monotherapy considered as an acceptable first-line choice among patients whose tumors test positive for EGFR protein.

Gefitinib is largely unavailable in the United States, except through a special program called the Iressa Access Program.

Other updated recommendations include:

► A caution against using first-line erlotinib (Tarceva) or gefitinib in patients without a demonstrated activating EGFR mutation.

► A recommendation to add bevacizumab (Avastin) (15 mg/kg every 3 weeks) to a first-line carboplatin/paclitaxel combination therapy until disease progression, except in patients with squamous cell carcinoma histologic type, brain metastasis, clinically significant hemoptysis or cardiovascular disease, inadequate organ function, ECOG (Eastern Cooperative Oncology Group) performance status greater than 2, therapeutic anticoagulation, or medically uncontrolled hypertension.

► A designation of acceptable, evidence-based second-line chemotherapy options, including docetaxel, erlotinib, gefitinib, or pemetrexed in patients with adequate performance status, regardless of age, in the face of disease progression or completion of a first-line platinum-based regimen.

► An option of erlotinib as third-line chemotherapy in patients with performance status 0 to 3 who have not previously been exposed to erlotinib or gefitinib. The choice of other third-line options should be considered within the context of clinical trials, experimental therapy, and best supportive care, the guideline suggests.

Elderly patients, those with limited vitality, and minorities receive special attention in the updated guideline, which advocates chemotherapy in the vast majority of patients with stage IV cancer, including those with ECOG performance status of 0, 1, "and possibly 2."

FOR THE FIRST TIME, THE GUIDELINE ADVOCATES CONSIDERATION OF AGENTS BASED ON EGFR STATUS.

Evidence supports the use of single-agent chemotherapy, and possibly even combination chemotherapy, in patients with an ECOG performance status of 2, the authors concluded, extending the patient groups considered for care beyond palliation.

Patients with an ECOG performance status of 2 are ambulatory and capable of self-care, but unable to work. They may be able to be "up and about" only slightly more than half of their waking hours.

"The evidence does not support the selection of a specific first-line chemotherapy drug (…[or] specific second-line) chemotherapy drug or combination based on age alone," the guideline states.

The guideline also emphasizes improved patient communication, which is hoped to improve disparities in outcomes among patients of different ethnic and racial groups.

Sessions specifically aimed at communicating options are recommended, with the "clinician … present[ing] the patient with a personalized description of his or her individual risks and benefits."

Such efforts might improve outcomes in African Americans, for example, who receive first-line chemotherapy for stage IV NSCLC only 36% of the time.

A number of the authors of the updated ASCO guidelines disclosed potentially relevant financial conflicts of interest related to pharmaceutical companies that manufacture oncologic drugs. ■

The new ASCO guideline, along with decision aid tools, is available online at www.asco.org/guidelines/nsclc.

values than many full-term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life. In limited clinical experience, 5 out of 6 (83%) pediatric patients with infections due to Gram-positive pathogens with MICs of 4 µg/mL treated with ZYVOX had clinical cures. However, pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response. **Geriatric Use** Of the 2046 patients treated with ZYVOX in Phase 3 comparator-controlled clinical trials, 589 (29%) were 65 years or older and 253 (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

ADVERSE REACTIONS Adult Patients The safety of ZYVOX formulations was evaluated in 2046 adult patients enrolled in seven Phase 3 comparator-controlled clinical trials, who were treated for up to 28 days. In these studies, 85% of the adverse events reported with ZYVOX were described as mild to moderate in intensity. The incidence (%) of adverse events reported in at least 2% of patients treated with either ZYVOX (n=2046) or all comparators† (n=2001) in these trials were as follows: diarrhea 8.3 and 6.3; headache 6.5 and 5.5; nausea 6.2 and 4.6; vomiting 3.7 and 2.0; insomnia 2.5 and 1.7; constipation 2.2 and 2.1; rash 2.0 and 2.2; dizziness 2.0 and 1.9; and fever 1.6 and 2.1 respectively. The most common adverse events in patients treated with ZYVOX were diarrhea (incidence across studies: 2.8% to 11.0%), headache (incidence across studies: 0.5% to 11.3%), and nausea (incidence across studies: 3.4% to 9.6%). The percent of drug-related adverse events in at least 1% of adult patients in a trial involving the treatment of uncomplicated skin and skin structure infection comparing ZYVOX 400 mg q12h (n=548) to clarithromycin 250 mg q12h (n=537) were 25.4 and 19.6 respectively. The percent of patients discontinuing drug due to drug-related adverse events‡ were 3.5 and 2.4 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 5.3 and 4.8; nausea 3.5 and 3.5; headache 2.7 and 2.2; taste alteration 1.8 and 2.0; vaginal moniliasis 1.6 and 1.3; fungal infection 1.5 and 0.2; abnormal liver function tests 0.4 and 0.0; vomiting 0.9 and 0.4; tongue discoloration 1.1 and 0.0; dizziness 1.1 and 1.5; and oral moniliasis 0.4 and 0.0 respectively. The percent of drug-related adverse events in at least 1% of adult patients in all other indications of ZYVOX 600 mg q12h (n=1498) versus all other comparators§ (n=1464) with at least 1 drug-related adverse event was 20.4 and 14.3 respectively. The percent of adult patients discontinuing due to drug-related adverse events‡ was 2.1 and 1.7 respectively. The incidence of drug-related adverse events occurring in >1% of adult patients were diarrhea 4.0 and 2.7; nausea 3.3 and 1.8; headache 1.9 and 1.0; taste alteration 0.9 and 0.2; vaginal moniliasis 1.0 and 0.4; fungal infection 0.1 and <0.1; abnormal liver function tests 1.3 and 0.5; vomiting 1.2 and 0.4; tongue discoloration 0.2 and 0.0; dizziness 0.4 and 0.3; and oral moniliasis 1.1 and 0.4. Other adverse events reported in Phase 2 and Phase 3 studies included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. **Pediatric Patients** The safety of ZYVOX formulations was evaluated in 215 pediatric patients ranging in age from birth through 11 years, and in 248 pediatric patients aged 5 through 17 years (146 of these 248 were age 5 through 11 and 102 were age 12 to 17). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies, 83% and 99%, respectively, of the adverse events reported with ZYVOX were described as mild to moderate in intensity. In the study of hospitalized pediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. The incidence of adverse events reported in ≥2% of pediatric patients treated for uncomplicated skin and skin structure infections‖ with ZYVOX (n=248) or cefadroxil (n= 251) were fever 2.9 and 3.6; diarrhea 7.8 and 8.0; vomiting 2.9 and 6.4; rash 1.6 and 1.2; headache 6.5 and 4.0; upper respiratory infection 3.7 and 5.2; nausea 3.7 and 3.2; trauma 3.3 and 4.8; pharyngitis 2.9 and 1.6; cough 2.4 and 4.0; generalized abdominal pain 2.4 and 2.8; localized abdominal pain 2.4 and 2.8; loose stools 1.6 and 0.8; localized pain 2.0 and 1.6; skin disorder 2.0 and 0.0 respectively. The incidence of adverse events reported in ≥2% of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) in comparator-controlled trials were fever 14.1 and 14.1; diarrhea 10.8 and 12.1; vomiting 9.4 and 9.1; sepsis 8.0 and 7.1; rash 7.0 and 15.2; headache 0.9 and 0.0; anemia 5.6 and 7.1; thrombocytopenia 4.7 and 2.0; upper respiratory infection 4.2 and 1.0; nausea 1.9 and 0.0; dyspnea 3.3 and 1.0; reaction at site of injection or of vascular catheter 3.3 and 5.1; trauma 2.8 and 2.0; pharyngitis 0.5 and 1.0; convulsion 2.8 and 2.0; hypokalemia 2.8 and 3.0; pneumonia 2.8 and 2.0; thrombocythemia 2.8 and 2.0; cough 0.9 and 0.0; generalized abdominal pain 0.9 and 2.0; localized abdominal pain 0.5 and 1.0; apnea 2.3 and 2.0; gastrointestinal bleeding 2.3 and 1.0; generalized edema 2.3 and 1.0; loose stools 2.3 and 3.0; localized pain 0.9 and 0.0; and skin disorder 0.9 and 1.0. The percent of pediatric patients treated for uncomplicated skin and skin structure infections‖ with either ZYVOX (n=248) or cefadroxil (n=251) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 19.2 and 14.1 respectively. The percent of pediatric patients discontinuing due to a drug-related adverse event was 1.6 and 2.4 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 5.7 and 5.2; nausea 3.3 and 2.0; headache 2.4 and 0.8; loose stools 1.2 and 0.8; vomiting 1.2 and 2.4; generalized abdominal pain 1.6 and 1.2; localized abdominal pain 1.6 and 1.2; eosinophilia 0.4 and 0.4; rash 0.4 and 1.2; vertigo 1.2 and 0.4 and pruritus at non-application site 0.4 and 0.0 respectively. The percent of pediatric patients treated for all other indications¶ with either ZYVOX (n=215) or vancomycin (n=101) and with ≥1 drug-related adverse event occurring in more than 1% of patients were 18.8 and 34.3 respectively. The percent of patients discontinuing due to a drug-related adverse event were 0.9 and 6.1 respectively. The incidence of drug-related adverse events reported in more than 1% of pediatric patients (and more than 1 patient) were diarrhea 3.8 and 6.1; nausea 1.4 and 0.0; loose stools 1.9 and 0.0; thrombocytopenia 1.9 and 0.0; vomiting 1.9 and 1.0; anemia 1.4 and 1.0; eosinophilia 1.4 and 0.0; rash 1.4 and 7.1; oral moniliasis 0.9 and 4.0; fever 0.5 and 3.0; pruritus at non-application site 0.0 and 2.0; and anaphylaxis 0.0 and 10.1# respectively. **Laboratory Changes** ZYVOX has been associated with thrombocytopenia when used in doses up to and including 600 mg every 12 hours for up to 28 days. In Phase 3 comparator-controlled trials, the percentage of adult patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 2.4% (range among studies: 0.3 to 10.0%) with ZYVOX and 1.5% (range among studies: 0.4 to 7.0%) with a comparator. In a study of hospitalized pediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count (defined as less than 75% of lower limit of normal and/or baseline) was 12.9% with ZYVOX and 13.4% with vancomycin. In an outpatient study of pediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with ZYVOX and 0.4% with cefadroxil. Thrombocytopenia associated with the use of ZYVOX appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). The platelet counts for most patients returned to the normal range/baseline during the follow-up period. No related clinical adverse events were identified in Phase 3 clinical trials in patients developing thrombocytopenia. Bleeding events were identified in thrombocytopenic patients in a compassionate use program for ZYVOX; the role of linezolid in these events cannot be determined (see **WARNINGS**). Changes seen in other laboratory parameters, without regard to drug relationship, revealed no substantial differences between ZYVOX and the comparators. These changes were generally not clinically significant, did not lead to discontinuation of therapy, and were reversible. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: hemoglobin (g/dL) 0.9 and 0.0; platelet count (x 10^3/mm^3) 0.7 and 0.8; WBC (x 10^3/mm^3) 0.2 and 0.6; neutrophils (x 10^3/mm^3) 0.0 and 0.2 respectively. The percent of adult patients with at least one substantially abnormal hematologic** value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: hemoglobin (g/dL) 7.1 and 6.6; platelet count (x 10^3/mm^3) 3.0 and 1.8; WBC (x 10^3/mm^3) 2.2 and 1.3 and neutrophils (x 10^3/mm^3) 1.1 and 1.2 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 400 mg q12h or clarithromycin 250 mg q12h for uncomplicated skin and skin structure infections were as follows: AST (U/L) 1.7 and 1.3; ALT (U/L) 1.7 and 1.7; LDH (U/L) 0.2 and 0.2; alkaline phosphatase (U/L) 0.2 and 0.2; lipase (U/L) 2.8 and 2.6; amylase (U/L) 0.2 and 0.2; total bilirubin (mg/dL) 0.2 and 0.0; BUN (mg/dL) 0.2 and 0.0; and creatinine (mg/dL) 0.2 and 0.0 respectively. The percent of adult patients with at least one substantially abnormal serum chemistry†† value in patients treated with ZYVOX 600 mg q12h or a comparator§ were as follows: AST (U/L) 5.0 and 6.8; ALT (U/L) 9.6 and 9.3; LDH (U/L) 1.8 and 1.5; alkaline phosphatase (U/L) 3.5 and 3.1; lipase (U/L) 4.3 and 4.2; amylase (U/L) 2.4 and 2.0; total bilirubin (mg/dL) 0.9 and 1.1; BUN (mg/dL) 2.1 and 1.5; and creatinine (mg/dL) 0.2 and 0.6 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: hemoglobin (g/dL) 0.0 and 0.0; platelet count (x 10^3/mm^3) 0.0 and 0.4; WBC (x 10^3/mm^3) 0.8 and 0.8; neutrophils (x 10^3/mm^3) 1.2 and 0.8 respectively. The percent of pediatric patients with at least one substantially abnormal hematologic‡‡ value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: hemoglobin (g/dL) 15.7 and 12.4; platelet count (x 10^3/mm^3) 12.9 and 13.4; WBC (x 10^3/mm^3) 12.4 and 10.3 and neutrophils (x 10^3/mm^3) 5.9 and 4.3 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a value in patients treated with ZYVOX or cefadroxil for uncomplicated skin and skin structure infections‖ were as follows: ALT (U/L) 0.0 and 0.0; lipase (U/L) 0.4 and 1.2; and creatinine (mg/dL) 0.4 and 0.0 respectively. The percent of pediatric patients with at least one substantially abnormal serum chemistry^a value in patients treated with ZYVOX or vancomycin for any other indication¶ were as follows: ALT (U/L) 10.1 and 12.5; amylase (U/L) 0.6 and 1.3; total bilirubin (mg/dL) 6.3 and 5.2; and creatinine (mg/dL) 2.4 and 1.0 respectively. **Postmarketing Experience** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported during postmarketing use of ZYVOX (see **WARNINGS**). Peripheral neuropathy, and optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX. Lactic acidosis has been reported with the use of ZYVOX (see **PRECAUTIONS**). Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, these events have also been reported in patients receiving shorter courses of therapy. Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and ZYVOX (see **PRECAUTIONS**). Convulsions have been reported with the use of ZYVOX (see **PRECAUTIONS**). Anaphylaxis, angioedema, and bullous skin disorders such as those described as Stevens Johnson syndrome have been reported. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to ZYVOX, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. **OVERDOSAGE** In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of linezolid was administered. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively.

* MDRSP refers to isolates resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

† Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; clarithromycin 250 mg PO q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‡ The most commonly reported drug-related adverse events leading to discontinuation in patients treated with ZYVOX were nausea, headache, diarrhea, and vomiting.

§ Comparators included cefpodoxime proxetil 200 mg PO q12h; ceftriaxone 1 g IV q12h; dicloxacillin 500 mg PO q6h; oxacillin 2 g IV q6h; vancomycin 1 g IV q12h.

‖ Patients 5 through 11 years of age received ZYVOX 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h. Patients 12 years or older received ZYVOX 600 mg PO q12h or cefadroxil 500 mg PO q12h.

¶ Patients from birth through 11 years of age received ZYVOX 10 mg/kg IV/PO q8h or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

These reports were of 'red-man syndrome,' which were coded as anaphylaxis.

** <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.

†† >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 x baseline for values abnormal at baseline.

‡‡ <75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline; <75% (<50% for neutrophils) of LLN and <75% (<50% for neutrophils, <90% for hemoglobin if baseline <LLN) of baseline for values abnormal at baseline.

^a >2 x Upper Limit of Normal (ULN) for values normal at baseline; >2 x ULN and >2 (>1.5 for total bilirubin) x baseline for values abnormal at baseline.

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EGFR Testing Is Urged for Advanced NSCLC

Patients who harbored EGFR mutations had longer progression-free survival with gefitinib or erlotinib.

BY ALICE GOODMAN
Elsevier Global Medical News

BERLIN — The drumbeat calling for routine testing of non–small cell lung cancer patients for mutations in the epidermal growth factor receptor grew louder at the joint congress of the European Cancer Organization and the European Society for Medical Oncology.

New and updated data from trials conducted largely (but not exclusively) in Asia showed gains in progression-free survival when patients with these mutations were treated with gefitinib (Iressa) or erlotinib (Tarceva), which are epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

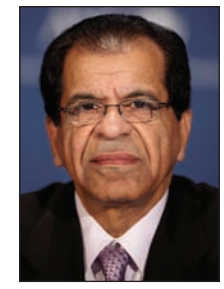
The consensus among the investigators was that EGFR testing should be usual care, especially in advanced patients with clinical characteristics suggesting that they would benefit from an EGFR TKI—namely, nonsmoking status, adenocarcinoma, Asian ethnicity, and female sex. Test results would then guide the selection of therapy: Patients with EGFR mutations would receive first-line therapy with either erlotinib or gefitinib, whereas those with wild-type EGFR would be treated with standard chemotherapy.

"Front-line EGFR TKI should become the new standard of care for patients with advanced NSCLC who harbor EGFR mutations, similar to HER2 testing and trastuzumab for breast cancer. This is the new treatment paradigm," Dr. Chandra P. Belani said in an interview after the meeting.

Evidence Favors Patients From Asia

Asian populations are more likely to have EGFR mutations, which occur in about 10% of NSCLC patients from the Western world and about 40% of those in Asia, according to Dr. Belani, the Miriam Beckner Distinguished Professor of Medicine at Pennsylvania State University, Hershey, and deputy director of the Penn State Hershey Cancer Institute in that city.

A key trial presented previously—the IRESSA Pan-Asia Study (IPASS) of 1,217 patients—showed that patients with EGFR mutations had longer progression-free survival when they were treated with gefitinib vs. chemotherapy. Dr. Tony Mok of the Chinese University of Hong Kong and colleagues reported that the testing of tissue samples from nonsmoking Asian patients showed that 60% of them harbored EGFR mutations. Progression-free survival and response rates were significantly improved in this group, whereas those without EGFR mutations fared better with chemotherapy in the study, which was sponsored by AstraZeneca (N. Engl. J. Med. 2009; 361:947-57).



EGFR tyrosine kinase inhibitors should be front-line therapy for patients with EGFR mutations.

DR. BELANI

At this year's joint congress, the following presentations reinforced the IPASS findings:

► An update of NEJ002 (A Randomized Phase III Study Comparing Gefitinib With Carboplatin Plus Paclitaxel for the First-Line Treatment of Non–Small Cell Lung Cancer With Sensitive EGFR Mutations), also from Asia, showed a doubling of median progression-free survival (10.4 months vs. 5.5 months) with first-line gefitinib vs. standard carboplatin plus paclitaxel chemotherapy in patients with EGFR mutations. Despite a numerical improvement in survival on the gefitinib arm, this did not reach statistical significance in the data presented by Dr. Akira Inoue of Tohoku University Hospital in Sendai, Japan, and colleagues. (Most patients who were assigned to the gefitinib arm were crossed over to chemotherapy at disease progression, Dr. Belani noted.)

► Dr. Junji Tsurutani of Kinki University in Osakasayama, Japan, presented the first data from the West Japan Thoracic Oncology Group (WJTOG) 3405 trial. This randomized, open-label study in 177 Asian NSCLC patients who harbored EGFR mutations found prolonged median progression-free survival with first-line gefitinib vs. a standard platinum-containing doublet (9.2 months vs. 6.3 months).

► Dr. Jean-Yves Douillard of Centre René Gauducheau, Nantes, France, and colleagues from Europe, Asia, and the United States presented a pooled analysis of four studies of first-line gefitinib vs. a comparator: IPASS, ISEL (Iressa Survival Evaluation in Lung Cancer; Lancet 2005;366:1527-37), INTEREST (Gefitinib vs. Docetaxel in Previously Treated Non–Small Cell Lung Cancer; Lancet 2008;372:1809-18), and the V-15-32 trial (Gefitinib vs. Docetaxel in Previously Treated Japanese Patients With Non–Small Cell Lung Cancer; J. Clin. Oncol. 2008;26:4244-52). Focusing on 1,006 patients for whom tissue samples were available, the analysis showed a consistent benefit for gefitinib across all lines of therapies (first-, second-, and third-line therapy), and a greater benefit in Asians than in non-Asians.

Tissue Testing Available in CLIA Labs

At present, tissue samples are used for EGFR testing at Clinical Lab Improvement Amendments (CLIA)-certified laboratories. Some centers of excellence, including the University of Texas M.D. Anderson Cancer Center in Houston and Memorial Sloan-Kettering Cancer Center in New York, have their own labs for EGFR testing, and these labs are also CLIA certified, Dr. Belani said.

The Spanish Lung Cancer Group (SLCG) has been trying to develop a serum test as an alternative that can be used when sufficient tissue is not available for a sample. However, Dr. Rafael Rosell of the Catalan Institute of Oncology–Germans Trias i Pujol University Hospital, Barcelona, and his colleagues reported they have found that serum testing of EGFR is not as reliable as tissue testing, so tissue testing remains the best method for determining EGFR mutation status for now. This was based on a study of matched serum and tissue samples from patients who were treated with erlotinib as first- and second-line therapy.

If EGFR mutations are present at primary diagnosis, they will persist throughout the course of disease, according to Dr. Belani. Therefore, taking tumor tissue at diagnosis is viable for testing. The hitch is that not all insurance companies will reimburse for EGFR testing. If patients don't get tested for EGFR mutations, they are treated with chemotherapy. If they do get tested and are EGFR positive, insurance companies in the United States will not necessarily provide reimbursement for first-line EGFR TKI therapy.

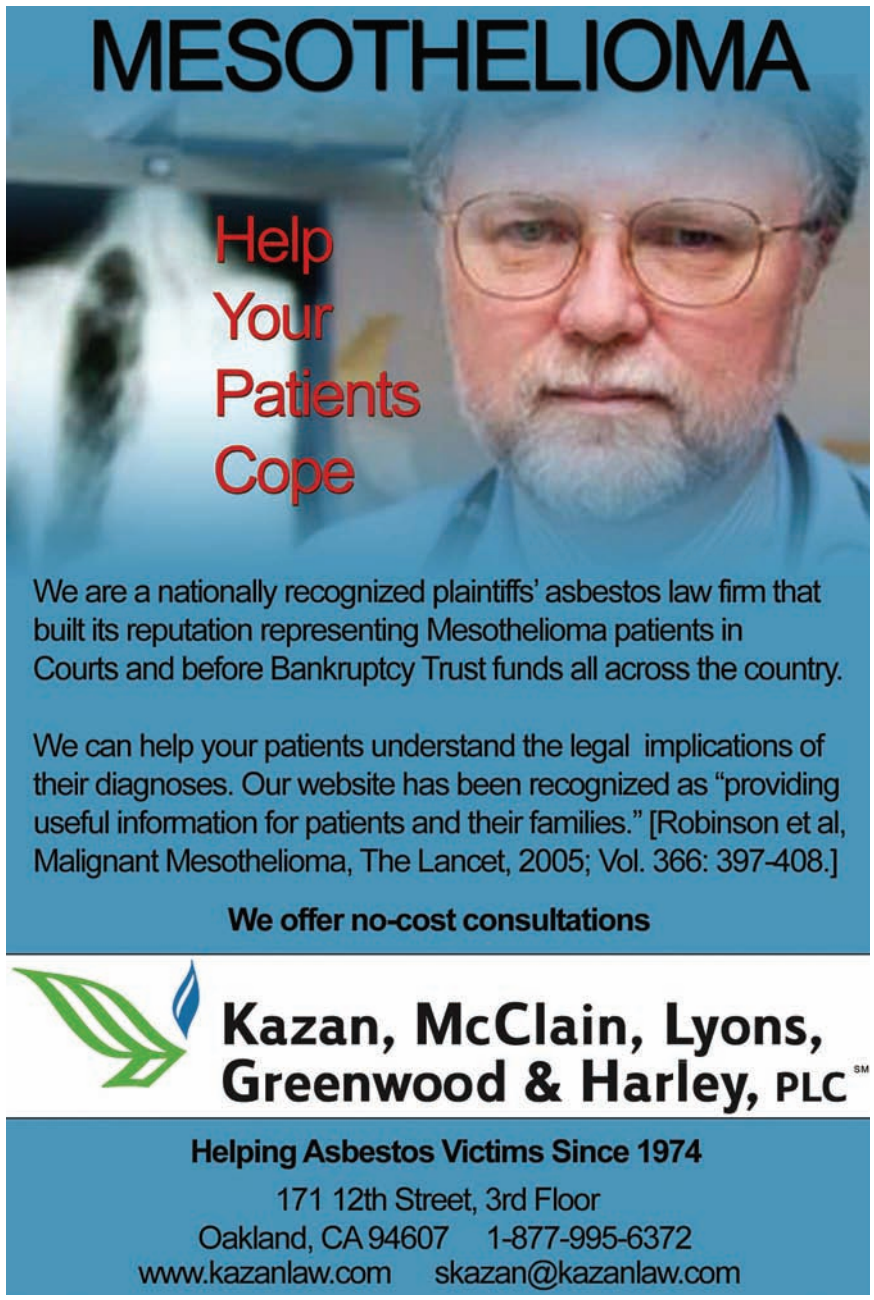
No First-Line Approval in U.S.

Erlotinib is the only TKI EGFR inhibitor that is approved in the United States for advanced NSCLC, and it is approved as second- and third-line—but not first-line—therapy. Gefitinib is used in Europe and Asia, where it is approved as first-line therapy for patients with EGFR-mutation–positive advanced NSCLC; it is available only to selected patients in the United States, however, under a risk-management program called the Iressa Access Plan.

"The discovery of EGFR mutations and their predictive value for response to erlotinib and gefitinib in patients who harbor these mutations came after erlotinib was approved by the FDA," Dr. Belani explained. It also followed the FDA's scaling back of the indication for gefitinib in 2005.

"Gefitinib should be resubmitted to the FDA for approval in patients with EGFR mutations on the basis of the available data from phase III trials performed outside" the United States, Dr. Belani urged.

"Based on the IPASS study, the NEJ002 study, and WJTOG 3405, patients with EGFR mutations should receive front-line therapy with either gefitinib or erlotinib," he said. ■



Small Series Sheds Light on Flu in Transplanted Lungs

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Early experience with pandemic influenza A(H1N1) in lung transplant recipients suggests the infection may result in chronic allograft dysfunction.

"Although our follow-up period is short, none of our patients [with H1N1 flu] have returned to their preinfection baseline respiratory status," Dr. Vivek N. Ahya noted at CHEST 2009, the annual meeting of the American College of Chest Physicians.

Dr. Ahya, medical director of the lung transplant program at the University of Pennsylvania, Philadelphia, reported on the five patients in the program who have developed laboratory-confirmed H1N1 flu to date. The experience gleaned from the small series suggests the infection in lung transplant patients may differ in important ways from the disease pattern in the general population.

The 5 affected patients are among roughly 300 lung transplant recipients who are currently being followed in the program. Three of the five patients became sick in June, and the other two fell ill in October.

One striking difference about disease presentation in these patients is that only one of the five had fever, whereas fever is a prominent feature in more than 90% of cases of H1N1 flu in the general population.

Instead, the lung transplant recipients presented with relatively nonspecific symptoms, including increasing shortness of breath, cough, and fatigue. Chest x-rays were reported as being clear in four of the five patients. However, CT scans reliably showed evidence of lung infection in the form of patchy ground-glass opacities.

Another notable point: The lung transplant patients with H1N1 flu were relatively old. One was 54 years old, and the rest were in their 60s. "We have not seen H1N1 yet in our young, healthy cystic fibrosis patients who've undergone lung transplantation, and hopefully we won't," Dr. Ahya continued.

Also noteworthy is the fact that all five affected patients had significant background comorbidities after transplantation. One became morbidly obese. Two others had multiple airway strictures that led to recurrent pneumonias. One patient had chronic donor organ rejection.

Another patient—the only one who died—developed H1N1 flu shortly after completing a course of radiotherapy for a squamous cell carcinoma in his native lung. That patient, the only one not immediately hospitalized for treatment, insisted on outpatient therapy. He had a DNR order in place because of his lung cancer, and he went to an outlying hospital when he suddenly deteriorated, so it's unclear whether his death was caused by H1N1 infection or something else, such as pulmonary embolism.

'We have not seen H1N1 yet in our young, healthy cystic fibrosis patients who've undergone lung transplantation.'

DR. AHYA

The first of the lung transplant recipients to develop H1N1 flu had a baseline FEV_1 of 1.27 L, 44% of the predicted value. When he presented with influenza, his FEV_1 had dropped to 0.7 L, or just 25% of the predicted value. Four months later, well after he had clinically recovered, his FEV_1 was 1.06 L, 37% of the predicted value.

Another patient who developed H1N1 flu in June is now being evaluated for retransplantation, he added.

Treatment of H1N1 flu included a reduction in immunosuppressive therapy, antibiotics, and a standard 5-day course of oseltamivir (Tamiflu). The antiviral agent was well tolerated.

One patient who was already colonized with *Pseudomonas* did well for the first 4 days on oseltamivir in the hospital, then deteriorated, developing septic shock and pneumonia in his native lung. He remains in the ICU on a ventilator.

Once the H1N1 vaccine becomes more widely available, Dr. Ahya said, the plan is to immunize all patients in the lung transplant program with a single dose.

He noted that there is evidence to suggest lung transplant patients may be more vulnerable than other solid organ recipients to seasonal influenza. Some years ago, University of Pittsburgh investigators reported that the rate of seasonal influenza was 41.8 cases per 1,000 person-years among their lung transplant patients, compared with 4.3 per 1,000 among kidney recipients and 2.8 per 1,000 for liver transplant patients (Am. J. Transplant. 2002;2:287-91).

The explanation for those findings is unclear. Lung transplant patients are typically more heavily immunosuppressed than are other solid organ recipients, and transplant physicians tend to look more closely for infections in that population, according to Dr. Ahya. ■

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Drug Combo Effective for H1N1 Flu-Related ARDS

BY BRUCE JANCIN
Elsevier Global Medical News

SAN DIEGO — Patients with suspected pandemic influenza A(H1N1)–associated acute respiratory distress syndrome responded favorably overall to an ICU treatment course of high-dose oseltamivir and prolonged low- to moderate-dose corticosteroids in a pilot study.

Eleven of 13 patients showed a marked improvement in lung injury scores by day 7, and the 15% in-hospital mortality rate was lower than expected in such a critically ill population, Dr. G. Umberto Meduri said at CHEST 2009, the annual meeting of the American College of Chest Physicians.

On the basis of these findings and the extensive basic science rationale in support of prolonged steroid therapy in acute respiratory distress syndrome, the French Ministry of Health has announced it will fund a randomized controlled trial of this treatment protocol in patients with H1N1 influenza–associated ARDS. However, the results won't be in until after the current seasonal outbreak of 2009 H1N1 flu has ebbed, said Dr. Meduri of the University of Tennessee, Memphis.

He reported on 13 consecutive patients who presented to an ICU in a tertiary-care hospital in Buenos Aires with suspected H1N1 influenza and hypoxemic respiratory failure during a 3-week period beginning June 24, 2009. Eight were in septic shock. Six had severe ARDS as defined by a PaO_2/FIO_2 (partial pressure of oxygen in arterial blood to the fraction of inspired oxygen) ratio of 120 or less and a positive end-expiratory pressure of at least 12 cm H_2O; patients this ill typically have an in-hospital mortality of about 55%, he said. By day 7 in the ICU, 11 of 13 patients showed significantly improved lung function as defined by at least a 1-point drop on the 4-point Lung Injury Scale, or a score below 2.

Monitoring for Delirium in ICU Gave No Benefit

SAN DIEGO — Daily systematic monitoring for delirium in a surgical ICU proved no more beneficial than did routine clinical judgment in identifying affected patients early and initiating effective therapy in a randomized trial.

These results raise a key, unanswered, question: Is delirium even a treatable condition? If not, early identification may be of little value, Dr. Ulrich H. Schmidt, FCCP, said at CHEST 2009, the annual meeting of the American College of Chest Physicians. "There is to date no validated active therapy for delirium," noted Dr. Schmidt of Massachusetts General Hospital, Boston. Delirium entails substantial morbidity, including longer hospital stays, as well as prolonged neurocognitive deficits post discharge in many cases.

There was no difference between the intervention and control groups in the duration of delirium.

DR. SCHMIDT

Dr. Schmidt and his colleagues hypothesized that daily administration of the Confusion Assessment Method for ICU patients (CAM-ICU), a validated screening tool (Crit. Care Nurse 2003;23:25-36), would result in earlier and more effective treatment of delirium than would clinical judgment alone.

To test this hypothesis, Dr. Schmidt had trained investigators administer the CAM-ICU daily to 283 patients after they had been in a surgical ICU for more than 48 hours. The findings for half of the patients were reported to the staff, but the information regarding the other half, which served as the control group, was withheld. Thus, staff had to rely on clinical judgment to detect delirium in controls.

In all, 35% of the 283 ICU patients developed delirium, as did 60% of the 116 who were mechanically ventilated. There was no difference between the intervention and control groups in the time from diagnosis to treatment of delirium, in the duration of delirium or mechanical ventilation, or in ICU length of stay.

—Bruce Jancin

Important Safety Information

Adcirca should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure. If a patient experiences anginal chest pain after taking Adcirca they should seek immediate medical attention.

Adcirca contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of Adcirca with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.

Patients with a known serious hypersensitivity to Adcirca should not take Adcirca.

PDE-5 inhibitors, including Adcirca, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing Adcirca, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of Adcirca to these patients is not recommended.

The use of Adcirca with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting).

Adcirca is metabolized predominantly by CYP3A in the liver. Use of Adcirca with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on Adcirca therapy that require treatment with ritonavir, Adcirca should be

Five patients were extubated by day 7, another 6 by day 14, and 2 later. The mean hospital length of stay was 18.7 days. Four patients developed ventilator-associated pneumonia as a complication of their ICU stay, and 5 nondiabetic patients required insulin therapy. All 13 survivors were discharged home with no supplemental oxygen requirement.

One patient, an alcoholic with cirrhosis who developed septic shock and severe ARDS, died from progressive multiorgan failure on day 15. The other death was believed to be caused by a pulmonary embolism in a patient with comorbid chronic obstructive pulmonary disease, an outcome that underscores the importance of continuing thrombotic prophylaxis at least until hospital discharge, Dr. Meduri noted.

Upon ICU admission, the treatment protocol entails starting oseltamivir (Tamiflu) via nasogastric tube at 150 mg twice daily for 5 days, followed by 75 mg twice daily for 3-5 days as dictated by the patient's clinical course.

While the protocol originally called for reserving methylprednisolone for those with severe ARDS and using hydrocortisone at 300 mg/day in the others, he now believes it's simpler to use methylprednisolone in all patients, giving higher doses to those who have severe ARDS.

The 15% in-hospital mortality rate was lower than expected in such a critically ill population.

DR. MEDURI

Upon ICU admission, patients receive a 60-mg IV bolus of methylprednisolone, then a continuous infusion at 60 mg/day for days 1-14, tapering to 30 mg/day on days 15-21, 15 mg/day on days 22-25, and 10 mg/day on days 26-28.

If, however, a patient presents with severe ARDS or worsens to that status at any point, the methylprednisolone dose is 1 mg/kg per day, tapered as detailed in Dr. Meduri's earlier randomized trial involving patients with early severe ARDS unrelated to H1N1 flu (CHEST 2007;131:954-63).

In the H1N1 pilot study, patients stayed on steroids for a mean of 21 days. ■

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- Adcirca 40 mg at 16 weeks compared with placebo
  - 33-meter mean improvement of 6MWD in patients with PAH[2]
  - 44-meter improvement in treatment-naive* patients[3]
  - 23-meter improvement in background bosentan subgroup, p=NS†
- 68% reduction in relative risk of clinical worsening with Adcirca 40 mg at 16 weeks compared with placebo[1,2]

Adcirca, a phosphodiesterase type 5 (PDE-5) inhibitor, is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability

ONCE-DAILY

adcirca™

tadalafil tablets

discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with Adcirca, start Adcirca at 20 mg once a day. Use of Adcirca with potent inducers of CYP3A, such as rifampin, should be avoided.
The use of Adcirca is not recommended for patients with severe renal or hepatic impairment. Please see full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment.
In rare instances, men taking PDE-5 inhibitors (including Adcirca) for ED reported a sudden decrease or loss of vision or hearing, or an erection lasting more than four hours. A patient who experiences any of these symptoms should seek immediate medical attention.
The most common side effects with Adcirca seen in the PHIRST-1 clinical trial were headache, myalgia, nasopharyngitis, flushing, respiratory tract infection, extremity pain, nausea, back pain, dyspepsia and nasal congestion.

Please see brief summary of Prescribing Information on next page.

*Treatment-naive defined as no treatment with a prostacyclin or analogue, L-arginine, phosphodiesterase inhibitor within 4 weeks prior to study initiation.

†Not significant.

References: 1. Adcirca [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2009. **2.** Galiè N, Brundage BH, Ghofrani HA, et al, for the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation.* 2009;119:2894-2903. **3.** Data on file, United Therapeutics Corporation.

ADCIRCA™ (tadalafil) Tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADCIRCA (tadalafil). Please review the full prescribing information prior to prescribing ADCIRCA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension

ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

CONTRAINDICATIONS

Concomitant Organic Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitrates and ADCIRCA on the nitric oxide/cGMP pathway.

Hypersensitivity Reactions

ADCIRCA is contraindicated in patients with a known serious hypersensitivity to tadalafil (ADCIRCA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

Discuss with patients the appropriate action to take in the event that they experience anginal chest pain requiring nitroglycerin following intake of ADCIRCA. At least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention.

PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors.

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

There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypotension (<90/50 mm Hg) or uncontrolled hypertension

Use with Alpha Blockers and Antihypertensives

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and alpha blockers may be affected by other variables, including intravascular volume depletion and use of other antihypertensive drugs.

Use with Alcohol

Both alcohol and tadalafil are mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects are increased.

Use with Potent CYP3A Inhibitors or Inducers

Co-administration of ADCIRCA in Patients on Ritonavir

In patients receiving ritonavir for at least one week, start ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Co-administration of Ritonavir in Patients on ADCIRCA

Avoid use of ADCIRCA during the initiation of ritonavir. Stop ADCIRCA at least 24 hours prior to starting ritonavir. After at least one week following the initiation of ritonavir, resume ADCIRCA at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Use in Renal Impairment

In patients with mild or moderate renal impairment

Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment

Avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Hepatic Impairment

In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B)

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCIRCA.

In patients with severe hepatic cirrhosis (Child-Pugh Class C)

Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCIRCA.

Effects on the Eye

Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors.

Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Hearing Impairment

Physicians should advise patients to seek immediate medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Combination with Other PDE5 Inhibitors

Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

Prolonged Erection

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention.

ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease).

Effects on Bleeding

PDE5 is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

ADVERSE REACTIONS

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

• Hypotension • Vision loss • Hearing loss • Priapism

Clinical Trials Experience

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

Tadalafil was administered to 398 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients.

In the placebo-controlled study, the most common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥ 9% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2%

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Headache	15	32	42
Myalgia	4	9	14
Nasopharyngitis	7	2	13
Flushing	2	6	13
Respiratory Tract Infection (Upper and Lower)	6	7	13

TABLE 1: Treatment-Emergent Adverse Events Reported by ≥ 9% of Patients in ADCIRCA and More Frequent than Placebo by 2% (cont)

EVENT	Placebo (%) (N=82)	ADCIRCA 20 mg (%) (N=82)	ADCIRCA 40 mg (%) (N=79)
Pain in Extremity	2	5	11
Nausea	6	10	11
Back Pain	6	12	10
Dyspepsia	2	13	10
Nasal Congestion (Including sinus congestion)	1	0	9

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.

Cardiovascular and cerebrovascular — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palpitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Body as a whole — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis

Nervous — Migraine, seizure and seizure recurrence, and transient global amnesia

Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion

Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

Otologic — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Urogenital — Priapism.

DRUG INTERACTIONS

Potential for Pharmacodynamic Interactions with ADCIRCA

Nitrates

Do not use ADCIRCA in patients who are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life–threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

Alpha-Blockers

PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.

Antihypertensives

PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood–pressure–lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

Alcohol

Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure–lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

Potential for Other Drugs to Affect ADCIRCA

Ritonavir

Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

Other Potent Inhibitors of CYP3A

Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA.

Potent Inducers of CYP3A

For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA.

Potential for ADCIRCA to Affect Other Drugs

Cytochrome P450 Substrates

Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan).

Aspirin

Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

P-glycoprotein *(e.g., digoxin)*

Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

Non–teratogenic effects

Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

Nursing Mothers

It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

Renal Impairment

For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability.

In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Hepatic Impairment

Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

OVERDOSAGE

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

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H1N1 Mortality Highest in Elderly, Mexican Data Show

BY HEIDI SPLETE
Elsevier Global Medical News

Adults aged 60 years and older were more likely to die from the pandemic influenza A(H1N1) virus than were younger individuals, during the first wave of the outbreak in Mexico, based on data from nearly 7,000 cases of H1N1 influenza.

The results were published online in the Lancet.

To explore protective factors and risk factors for infection, severe illness, and death related to the 2009 H1N1 virus, Dr. Santiago Echevarria-Zuno of the Instituto Mexicano del Seguro Social (Mexican Institute for Social Security) in Mexico City and colleagues reviewed data for 63,479 people with influenza-like illness collected from a national influenza surveillance system between April 28 and July 31, 2009. Of those, 6,945 (11%) were confirmed H1N1 infections (Lancet 2009 [doi: 10.1016/S0140-6736(09)61638-X]).

THE CONFIRMED H1N1 MORTALITY RATE WAS 10.3% IN PERSONS OLDER THAN 70 YEARS, AND 5.7% IN THOSE AGED 60-69 YEARS.

"Infants and people aged 10-19 years were at increased risk of infection, but disease was more severe in infants and those older than 60 years than in other age groups," the researchers noted. Similar to reports from the United States, patients with chronic diseases and pregnant women were at increased risk of severe illness, as were individuals for whom hospital admission was delayed.

A total of 63 confirmed H1N1 deaths occurred in the study population. Individuals with chronic conditions were at increased risk of death from H1N1, the researchers noted. Chronic conditions reported in the fatal cases from the study population were hypertension, obesity, and diabetes.

The confirmed H1N1 mortality rate was 10.3% in persons older than 70 years, 5.7% in those aged 60-69 years, and 4.5% in those aged 50-59 years. On the other end of the age spectrum, the confirmed H1N1 mortality rate was 1.6% in infants younger than 1 year, but 0.2% in children age 1 year through 19 years. The confirmed H1N1 mortality rate was 0.9% in the 20-29–year age group, 2.0% in the 30-39–year age group, and 2.7% in the 40-49–year age group.

The deaths in the study population included four pregnant women aged 20-31 years. All four received oseltamivir within 5-9 days of the start of their symptoms, and all four had dyspnea. One pregnant patient was a smoker, one had hypothyroidism, and one was obese.

The most often reported symptoms of H1N1 infection were fever, cough, headache, muscular pain, and rhinorrhea, the researchers said. Factors that predicted hospital admission and death included dyspnea, tachypnea, cyanosis, and confinement to bed.

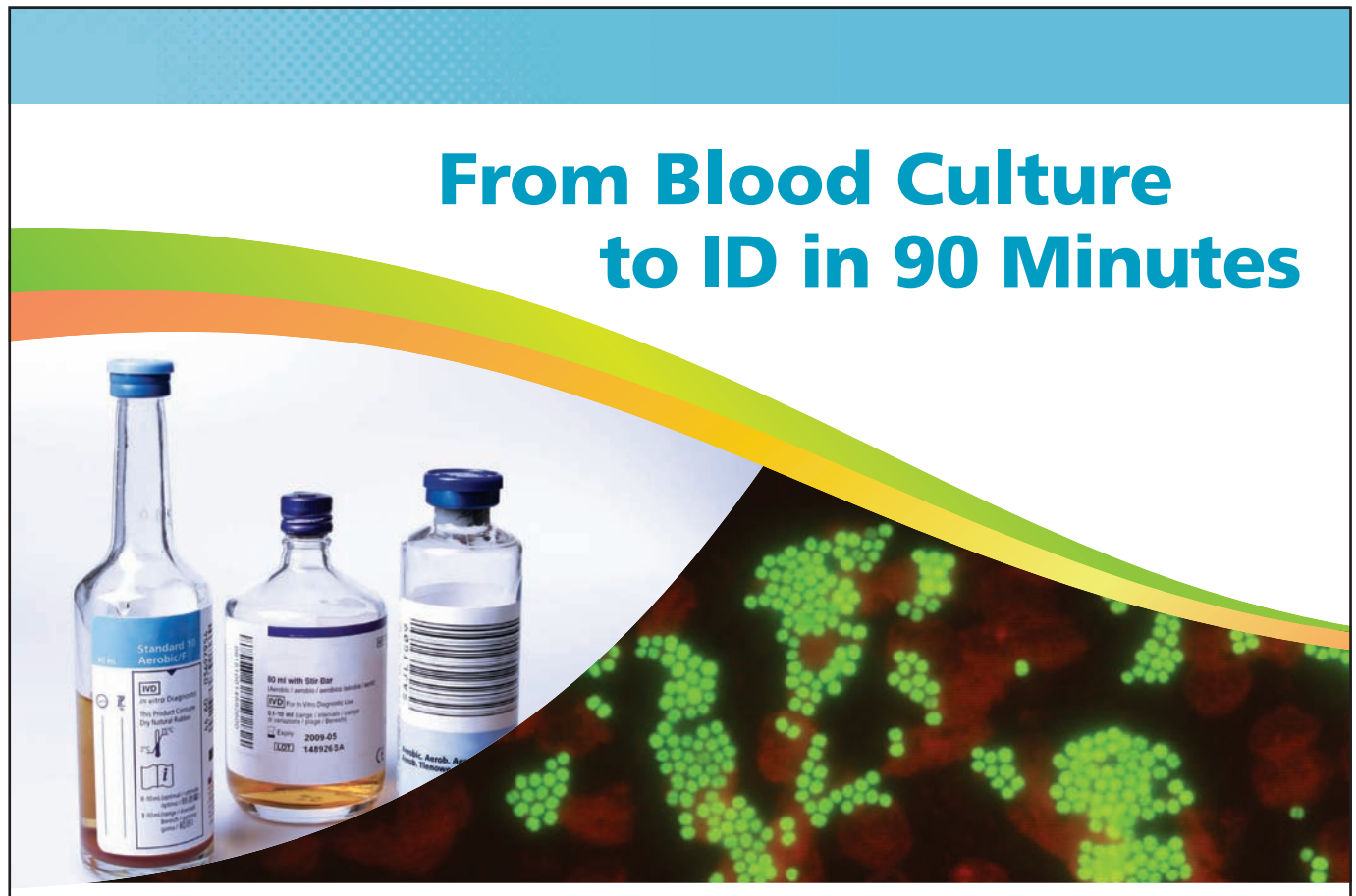
The results were limited by incomplete data in some cases, as well as a lack of data on whether infection control measures such as school closings reduced the spread of disease, the researchers said.

Overall, the risk of infection was 35% lower among individuals who had been vaccinated for seasonal flu, but a protective effect of seasonal flu vaccination against H1N1 remains controversial, the researchers noted.

"A significant finding in today's report was that the infection risk was highest in children, but the disease was more severe (i.e., higher risk of death) in people older than 60 years," noted the authors of an accompanying editorial, Dr. V. Alberto Laguna-Torres of the U.S. Naval Medical Research Center Detachment in Lima, Peru, and Dr. Jorge Gomez Benavides of San Marcos University in Lima (Lancet 2009 [doi: 10.1016/S0140-6736(09)61916-4]).

But the results also were limited by challenges of influenza surveillance, they noted, because not all patients who are ill seek medical care, and not all patients who sought care were tested for the H1N1 virus specifically.

The researchers declared no financial conflicts of interest. ■



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- **Reduce mortality rates** for *E. faecium* bacteremia[2]
- **Improve antifungal selection** for candidemia[3]
- **Reduce unnecessary vancomycin** use, LOS and costs due to blood culture contamination[4]

Species Distribution in Positive Blood Cultures

Gram Stain - Dilemma	Species	% of Group
GPCC (55%) Infection vs. Contamination	*S. aureus*	25%
	Coagulase-Negative Staph	75%
GPCPC (15%) Ampicillin and Vancomycin Resistance	*E. faecalis*	40%
	E. faecium	25%
	Streptococcus sp.	35%
GNR (20%) *P. aeruginosa* vs. non-*P. aeruginosa*	*E. coli*	35%
	K. pneumoniae	20%
	P. aeruginosa	15%
	Other GNRs	30%
Yeast (5%) Echinocandin vs. Fluconazole	*C. albicans*	50%
	C. glabrata	20%
	C. parapsilosis	15%
	Other *Candida* sp.	15%
Other (5%)		

1. Ther Clin Risk Manag. 2008 Jun;4(3):637-40.
2. Antimicrob Agents Chemother. 2008 Oct;52(10):3558-63.
3. Della-Latta et al. ECCMID 2008. Poster #P1382
4. J Antimicrob Chemother. 2006 Jul;58(1):154-8.

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Critical Care Commentary

ICU: The New Hospice

Why end-of-life communication training is increasingly important for critical care medicine.

Because 20% of Americans die in ICUs, critical care has become the new hospice. Consequently, intensivists find themselves, often without enthusiasm, in the role of palliative care physicians.

Reluctance to engage in ICU palliative care may be because, *prima facie*, critical care is about saving lives, rather than facilitating peaceful deaths. Additionally, dealing with death can be emotionally averse.

This is compounded by a paucity of end-of-life training within critical care medicine, resulting in deficits of communication and palliative skills.

There is widespread agreement that better end-of-life communication is a key ingredient in decision-making and implementing palliative care in the ICU.

In fact, physician-patient/family communication can be seen as an essential rate-limiting step, without which it is nearly impossible to institute ICU palliative care.

Better communication may also result in improved ICU patient outcomes. Data supporting these are considered in three areas: quality of death and dying, the emotional impact on next of kin, and institutional outcomes (length of stay, cost).

Dr. Neil Halpern, FCCP
Section Editor, *Critical Care Commentary*

Quality of Death and Dying

Assessing the quality of one's own ICU death is quite challenging for obvious reasons. Thus, observers, either family members or nurses, can rate the dying experience on a scale, such as the Quality of Death and Dying Scale.

Using this scale, rated by nurses, Curtis and coworkers demonstrated that quality of death and dying can be improved by a multifaceted intervention that includes clinician education, local champions, academic detailing, feedback to clinicians, and system support (Curtis et al. *Am J Respir Crit Care Med* 2008; 178:269).

Thus, a tailored intervention that includes elements of better communication may improve the dying experience.

Emotional Impact of an ICU on Next of Kin

Family members of patients who both survive or die in the ICU are psychologically distressed by the experience.

For example, 90 days after an ICU discharge, posttraumatic distress symptoms were seen in 29% of family members of patients who survived an ICU admission but increased to 50% in situations where the patient died.

Where next of kin participated in end-of-life decision-making, 82% scored above threshold for posttraumatic distress and also had higher rates of anxiety and depression (Azoulay et al. *Am J Respir Crit Care Med* 2005; 171:987). The emotional trauma of an ICU admission on next of kin thus presents a compelling reason to improve the quality of an ICU death.

A recent randomized controlled trial found that a rather simple intervention, a schema for conducting a family meeting and a brochure about what to expect from dying, reduced the rates of posttraumatic stress symptoms, depression, and anxiety in a grieving family member (Lautrette et al. *N Engl J Med* 2007; 356:469).

Easing the burden of grief, especially prolonged grief (with its 11% prevalence), might have a significant public health benefit (Prigerson et al. A case for inclusion of prolonged grief disorder in DSM-V. In: Stroebe et al, eds. *Handbook of Bereavement Research and Practice*. Washington, DC: American Psychological Association, 2008;165-185).

Imagine a husband with two young children whose wife recently died of cancer. Parenting is immeasurably more difficult in the presence of posttraumatic distress, depression, and anxiety. Connection to an emotionally absent father at a critical time of healing is also impeded.

Although improving post-ICU death outcomes has the potential to significantly impact the family, it is a new outcomes paradigm for critical care medicine.

Institutional Outcomes

The idea that so-called "soft" psychosocial interventions can positively impact ICU length-of-stay is quite remarkable. Curtis, for example, found that his multifaceted ICU intervention promoting palliative care implementation, described above, reduced ICU length-of-stay from a median of 7.2 to 5.8 days.

A recent study found that only 31% of patients with advanced cancer reported end-of-life discussions with their oncologists. Health-care costs in the last week of life for patients who had discussed end-of-life care were 36% less than for those patients who had not discussed end-of-life care. Survival was identical in both groups (Zhang et al. *Arch Intern Med* 2009; 169:480). Thus, better end-of-life communication saves health dollars because people make better treatment choices.

What Is Communication Skill Training?

Communication skills are seen as core competencies by major health-care organizations (Liaison Committee on Medical Education [LCME], Accreditation Council for Graduate Medical Education [ACGME], National Board of Medical Examiners [US Medical Licensing Examination]).

Simulation communication training has been increasingly adopted nationally (*eg*, University of Pittsburgh, Institute for Doctor-Patient Communication; Children's Hospital Boston, Program to Enhance Relational and Communication Skills; Temple University's Institute for Clinical Simulation and Patient Safety; Center for Communication and Medicine, Northwestern University Feinberg School of Medicine; Children's National Medical Center) and internationally (Israel, Australia, United Kingdom).

Cancer communication is, by nature, emotionally saturated, especially in regards to discussing dying. Most of us, given the choice, will avoid it.

Recognizing this, Memorial Sloan-Kettering Cancer Center has developed the Communication Skills Research and Training Laboratory (Comskil Lab), the only dedicated communication training facility at a comprehensive cancer center. A modular approach has been designed to help simulate dilemmas, such as breaking bad news, discussing prognosis, and discussing ICU end-of-life care.

The ICU modules focus on family communication rather than the traditional doctor-patient model, because most ICU patients are incapacitated. Actors portray family members. Before and after the training sessions, skill levels are assessed using a 12-min standardized assessment that is videotaped and scored.

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This Month in *CHEST*: Editor's Picks

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

Procedure Videos Online

► **Whole Lung Lavage for Pulmonary Alveolar Proteinosis.** *By Dr. G. Michaud, et al.*
G/W EDITORIAL

► **A Video Says More Than A Thousand Words.** *By Dr. A. Ernst, FCCP; and Dr. G. Michaud.*

► **Prevalence and Progression of Osteoporosis in Patients With COPD: Results From TORCH.** *By Dr. G. T. Ferguson, FCCP, et al.*

► **Association Between ICU Admission During Morning Rounds and Mortality.** *By Dr. B. Afessa, FCCP, et al.*

► **Achieved Anticoagulation vs Prosthesis Selection for Mitral Mechanical Valve Replacement: A Population-Based Outcome Study.** *By Dr. T. Le Tourneau, et al.*

Topics in Practice Management

► **The Medicare Physician Quality Reporting Initiative: What Do Chest Physicians Need To Know?** *By Dr. M. L. Metersky, FCCP.*
G/W EDITORIAL

► **Physician Leadership for High Quality Care.** *By Dr. C. M. Clancy.*

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Different points in the dying trajectory are simulated (transition from curative to palliative goals of care, DNR discussions, withdrawal of life-extending treatments). A didactic program provides an evidence-based framework, and demonstration videos model proper communication techniques.

The steepest part of the learning curve comes from role-play, because training at this point is individualized to meet the physician's deficits. Video-assisted feedback allows for recognition of inefficient techniques, reflection, and practice of better strategies.

What are some of the typical skills that a physician might work on in communication training? One is the centrality of empathic communication.

When a family member is overwhelmed by emotion, such as distress or sadness, then the understanding and processing of the medical or prognostic data required for informed decision making is more difficult. Critical care medicine trainees learn to address these emotions first, prior to moving forward in the conversation.

There are many ways of ameliorating emotions: normalization ("It is normal to be upset …") and paraphrasing and repeating back ("So, what you are saying is that …"), but critical care medicine physicians seem to find silence or listening most difficult. Silence represents understanding and sharing in the pain of suffering.

Video feedback can palpably demonstrate the efficacy of timely silence. Physicians who tend to lecture patients/families are often not aware of this until they view themselves on video feedback. Doctors who talk less and listen more are actually perceived as being more empathic.

Communication training often addresses double-talk—physicians saying one thing when they mean another.

For example, discomfort talking directly about dying often drives physicians to use metaphors. "Would you like *everything* done?" is actually an attempt to say, "If you were close to death, we physicians would like to avoid futile resuscitation."

The problem is that patients/families understand "*everything*" to mean a comprehensive approach. The opposite of "*everything*" is understood to be a halfhearted approach. Nobody would want a halfhearted professional, such as a mechanic or banker on their team and certainly not a halfhearted physician.

Communication training can unpack the metaphor "everything," clarifying the real underlying issue, that CPR in dying cancer patients has an almost zero efficacy.

"Heroic measures" is another metaphor for futile CPR that is understood in divergent ways by physicians and patients/families.

Would you prefer physicians to use heroics or the opposite, "cowardly" measures? I would select heroic measures. It reminds me of the movie, "Saving Private Ryan."

But the real issue is physician discomfort discussing futile CPR and dying. This can be practiced in communication training, adding better lines to physicians' end-of-life communication scripts, which more accurately reflect their good intent.

End-of-Life Communication: A Dilemma in the Best of Institutions

I was shocked recently when training a group of Eastern European palliative care physicians. One broke down in tears during role-play— he had never told a patient that he or she was dying. "Truth telling" is an old story in the West, so imagine my dismay when, 1 week later, I heard of a ventilated, brain dead patient, kept alive for weeks at a top US hospital. Earlier initiation of this painful negotiation would have helped the patient and family find their respective peace.

The physicians involved in this case were both competent and caring, yet they found it difficult to initiate the withdrawal of life-extending treatment conversation. Not wanting to disappoint the family, fears of litigation, a communication skill deficit, or cultural divergence may have impeded better communication. Nevertheless, earlier initiation of this painful negotiation would have helped the patient and family find their respective peace.

The need for ICU communication training is ubiquitous, even in the most prestigious medical institutions, because discussing death is so intrinsically difficult, even among kind-hearted, experienced critical care medicine physicians.

Although it seems obvious that communication training would be beneficial in the ICU setting, the challenge remains to demonstrate skill uptake and improved clinical outcomes. Currently, critical care medicine communication training is at an early, but exciting, stage of development. ■

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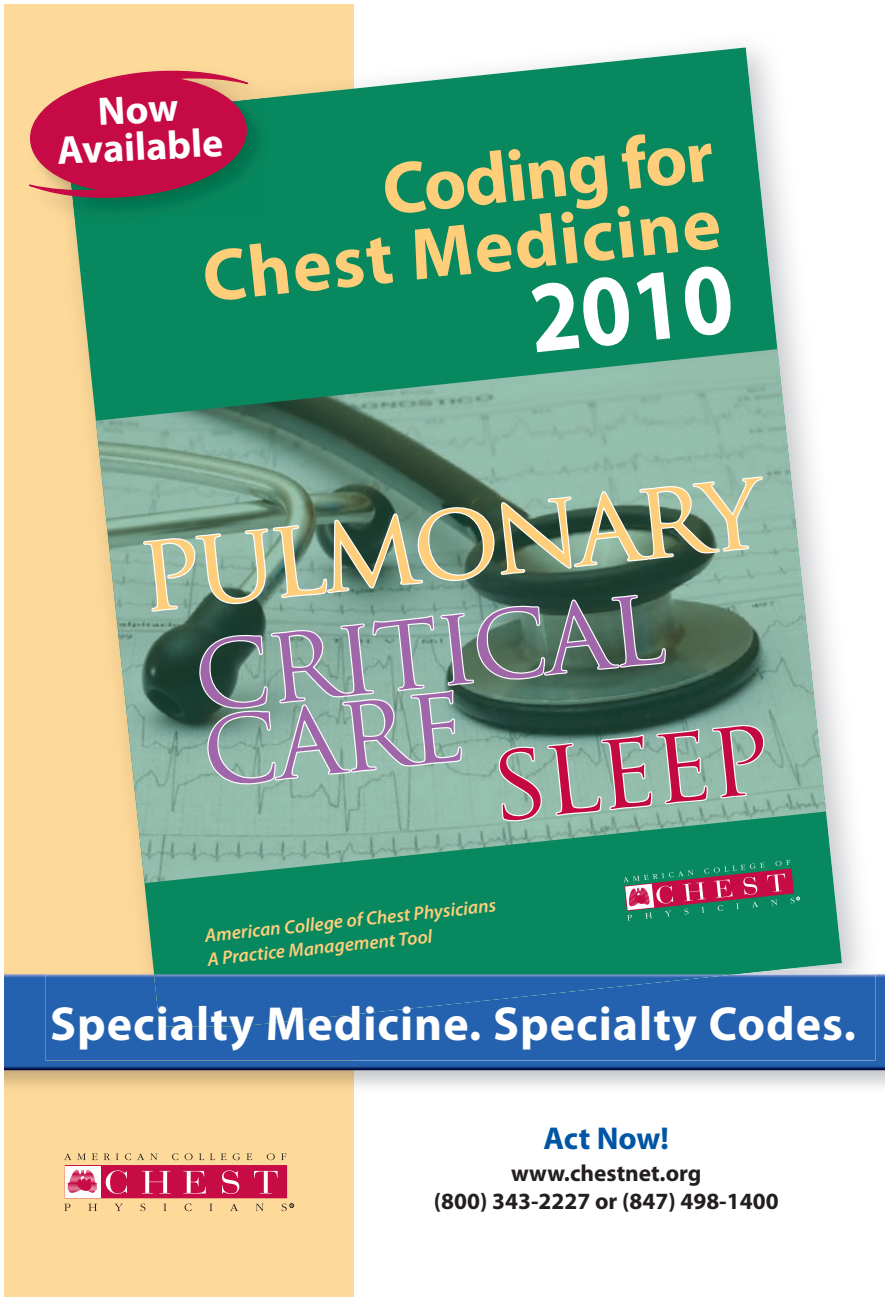

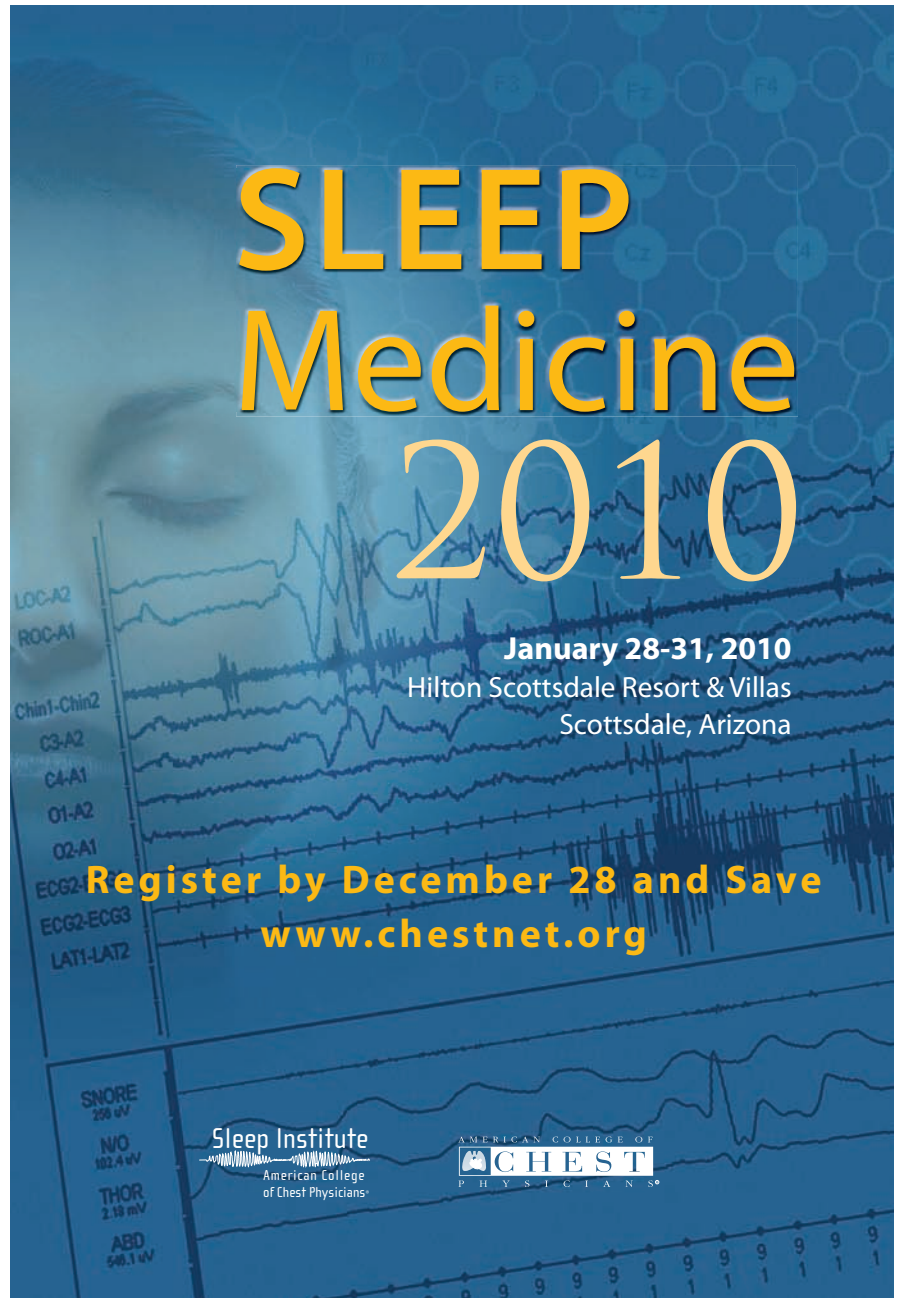

In Final Rule, CMS Eliminates Consultation Codes

The decision directly impacts the ACCP membership.

The American College of Chest Physicians (ACCP) closely reviewed the Medicare Physician Fee Schedule (MPFS) proposed rule, and submitted written comments to CMS requesting that they remove the proposal to eliminate consultation codes or at least delay the implementation of the proposal.

Similar requests were also made by other medical specialty societies, including the American College of Physicians and the American Thoracic Society.

CMS released its final ruling regarding the 2010 MPFS on October 30, and unfortunately, chose to proceed with elimination of payment for consultation codes as of January 1, 2010. This is a decision in the final rule that directly impacts the ACCP membership.

Robert DeMarco, MD, FCCP, Vice Chair Practice Management Committee and ACCP Governor for Ohio, wrote his Ohio constituents, "This does not mean that we will not be able to do consultative work; we will need to bill these services with different CPT codes."

The following facts will help you understand how this new rule will change the way you will now document for what previously coded as consultations:

- Consultation codes **99241-99245** (outpatient/office) and **99251-99255** (inpatient) are **eliminated** for Medicare effective January 1, 2010. The telehealth consultation G-codes (**G0425-G0427**) will not be eliminated.
- In 2010, consultations in the office/outpatient setting will be coded using the existing CPT codes for new (**99201-05**) or established (**99211-15**) patients. In the inpatient hospital setting, the existing CPT codes for initial hospital care (**99221-23**) will be used and initial nursing facility codes (**99304-06**) will be used in the nursing facility consultations.
- A modifier will be developed to differentiate the admitting physician of record from the consultants for initial hospital inpatient and nursing facility admissions.
- Change would be budget neutral. Payment for outpatient/office codes will increase 6% from the same code payment in 2009. Initial hospital and facility visit E/Ms will increase 2% from the same code payment in 2009.
- Increases to other E/Ms will increase payment for ALL E/M coding, not just when reporting a former consultation.
- No information has been forthcoming from other third-party payers about reporting consultations in 2010. However, CMS stated in the MPFS, "If the primary payer does continue to recognize those codes [consultation codes], the physician will need to decide whether to bill the primary payer using visit codes, which will preserve the possibility of receiving a secondary Medicare payment, or to bill the primary payer with the consultation codes, which will result in a denial of payment for invalid codes." Ultimately, it is likely that most third party contracts will need to be renegotiated as these payers often follow the example set by CMS.

Individual Practice Analysis

To determine the effect of the loss of the consultation codes, each practice needs to estimate the percentage of Medicare consultations previously performed in a year. Members should be aware that "consultations" from a specialist will continue to be requested. However, they will now be billed using different CPT codes as annotated above. This may result in loss, gain, or no significant change in your practice revenues, dependent upon your payer mix.

A detailed explanation of the changes in the consultative services coding is provided in the ACCP publication *Coding for Chest Medicine 2010*—available in the ACCP store at www.chestnet.org. ■

This Month in PCCU

- **Treatment of Lung Cancer in Older Patients.** *By Dr. Scott Gettinger*
- **Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension: A Review.** *By Dr. Steven Nathan, FCCP*

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Board of Regents Approves Realignment of ACCP NetWorks and Institutes

BY TRACY GOODE, MBA, MHSA
Vice President, Member Activities

At CHEST 2009 in San Diego, the ACCP Board of Regents approved three organizational changes to the ACCP NetWorks:

- The Practice Administration NetWork and Private Practice NetWork merged to become the Practice Operations NetWork.
- The Critical Care NetWork merged with the Critical Care Institute.
- The Sleep Medicine NetWork merged with the Sleep Institute.

All of these changes became effective at the close of CHEST 2009.

The Practice Administration and Private Practice NetWorks have always shared common goals and issues, as well as many common members. The two groups were already working together in many ways. The merger achieves resource and administrative efficiencies, as well as improved strength and effectiveness for its members.

The Practice Operations NetWork will stimulate the exchange of ideas and knowledge between physicians and practice administrators. The NetWork seeks to increase quality patient outcomes, aid in the delivery of prompt service, and maximize reimbursement by optimizing practice efficiency. The areas of focus are staffing, billing, coding, system infrastructure, and performance measurement. The NetWork is open to all members practicing clinical medicine in both academic and traditional private practice settings and to administrative and clinical staff responsible for the operations of the practice.

The 2010 co-chairs of the Practice Operations NetWork are Philip Marcus, MD, FCCP, and Michael McCormick, RRT.

The Critical Care NetWork and Institute merger resulted in one group that will retain the Critical Care Institute name and function as a member of the Council of NetWorks. Similarly, the Sleep Medicine NetWork and Sleep Institute merger resulted in one group that will retain the Sleep Institute name and function as a member of the Council of NetWorks. (The "Critical Care NetWork" and the "Sleep Medicine NetWork" names will no longer be used.)

Both of these combinations will harness the strength in the number of members of the two NetWorks with the brand recognition that has been established by the Institutes. They will continue to collaborate with sister societies, industry partners, and other organizations on various projects, as well as conduct the standard business of NetWorks, such as development of sessions for CHEST annual meetings. Furthermore, the mergers will improve resource and staffing efficiencies and eliminate redundancies between the NetWorks and Institutes.

The 2010 co-chairs of the Critical Care Institute are Jeffery Vender, MD, FCCP, and LTC Alexander Niven, MC, USA, FCCP. The 2010 co-chairs of the Sleep Institute are Barbara Phillips, MD, FCCP, and Teofilo Lee-Chiong, MD, FCCP.

The leaders of all three of these groups agree that it is the right time to make these transitions. They are working together to integrate their activities and improve ACCP's presence in critical care, sleep, and the business of medicine.

For more information about the NetWorks and Institutes, contact networks@chestnet.org. ■

Al Lever Honored at ERS Congress

At a speakers' dinner gathering in the City Hall of Vienna, about 500 distinguished guests from around the world joined Professor O. C. Burghuber, FCCP, Congress Chair, in acknowledging retiring Executive Vice President and CEO of the ACCP, Al Lever, for his leadership commitments.

Professor Burghuber announced Mr. Lever's retirement to the audience and commented that the ERS, in particular, appreciated his kind commitment to share his immense knowledge and experience with the leadership of ERS.

"He truly became a most valuable person within the society, known to many of us—people in the pulmonary field worldwide," noted Burghuber. "We wish him the best for his next future steps and hope to keep in contact with him, as well with the ACCP, to further improve our relationship and common interests." ■

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"Participating in the ACCP community brings many benefits. People who become actively involved tend to get enough satisfaction to become more involved. Take this as a call to action to participate in the work and activities of the ACCP."

Al Lever, MA, FCCP(Hon)

"A focus of well-being for all those involved with promoting health has motivated me to be involved."

Norine Lever

A Legacy of Leadership

Al and Norine Lever have an 18-year history of noteworthy leadership on behalf of the ACCP and The CHEST Foundation. As CEO of the ACCP, Al has maintained high standards and has adhered to the ACCP mission to promote the prevention and treatment of diseases of the chest through leadership, education, research, and communication. Norine has been actively involved through The CHEST Foundation's Ambassadors Group, which she conceived to volunteer, network, and educate on behalf of The Foundation.

Continuing the Legacy

To honor the Lever's accomplishments and successes as leaders, The CHEST Foundation has established the Al and Norine Lever Honorary Endowment Fund to foster exceptional leadership among health-care professionals. Show your appreciation for Al and Norine and continue their legacy by donating to this important fund.

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Al Jahra, Kuwait

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Coming Soon: CHEST 2009 Highlights

Ready to relive all the action from last month's CHEST 2009 meeting in San Diego? Looking for a chance to find out what you missed?

Watch for a wrap-up of all the news and highlights from the ACCP's annual meeting in the January issue of *CHEST Physician*!

COURTESY ACCP

PRACTICE MANAGEMENT

Medicare Final Rules You Need To Know

New/Revised CPT Codes Valued for 2010

CMS accepted CPT surveyed code values for:

- **31626** bronchoscopic placement of fiducial markers
- **31627** navigational bronchoscopy
- **32560** revised pleurodesis code
- **32561**, **32562** new fibrinolysis codes
- **94011-94013** infant PFT codes
- **92570**, **92571** two revised Photodynamic Therapy codes.

We thank all the members who participated in the surveys for these 10 new codes.

Practice Information Survey

The Practice Information Survey data was accepted. Pulmonary practice expense per hour (PE/hr) increased from $44.63 to $55.26. Overall impact of the final Medicare Physician Fee Schedule rule for pulmonary medicine was 0%, which means the increases from participation in the practice expense survey offset the elimination of coverage for reporting the consultation codes.

Thank you to the members that participated in the random AMA survey that provided sufficient data to increase the practice expense per hour for pulmonary medicine.

Pulmonary Rehabilitation

CMS did clarify that this rule does not impact the Local Coverage Determination (LCD) policies for non-COPD conditions, and as current LCD coverage allows it, providers can continue to provide and bill for services provided to non-COPD patients under existing LCDs, until such time a National Coverage Determination (NCD) is adopted. It is advisable to take direction from the Medicare Administrative Contractors (MACs)/carriers for reporting these services for non-COPD diagnoses.

Effective January 1, 2010, for moderate, severe, very severe COPD (Gold II-IV), report only **G0424, Pulmonary rehabilitation, including exercise (includes monitoring), per hour, per session.**

Medicare policy will include up to 2 sessions per day and will cover 36 sessions. At the MAC/carrier discretion, they may extend up to 36 additional sessions for medical necessity with a cap of 72 total sessions. A "supervising physician" must be immediately available and accessible for medical consultations and emergencies. Physical therapy/occupational therapy codes cannot be reported for pulmonary rehabilitation programs.

Physician Quality Reporting Initiative (PQRI) Claims-Based CAP Measures Group

Effective January 1, 2010, a Community-Acquired Pneumonia (CAP) Measures Group was approved for claims based reporting. Thirty patients would be reported in a one year period, or 15 patients if they represent 80% of the physician's pneumonia patients, or 8 patients if the measure is reported starting July 1 through December 31, 2010. The consecutive patient requirement for 2009 has been deleted. ■

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs [see **Nonclinical Toxicology**].

Nursing Mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration, Warnings and Precautions**].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight [see **Dosage and Administration**].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m² basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m² basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/ day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

• Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

• Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNg 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

• Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

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Revised August 2009

References for previous pages: 1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. August 2009. **2.** Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008;371:2093-2100. **3.** Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet*. 2001;358:1119-1123. **4.** Data on file, Actelion Pharmaceuticals.

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ACTELION

DNA Technology May Revolutionize Flu Vaccine

BY DOUG BRUNK
Elsevier Global Medical News

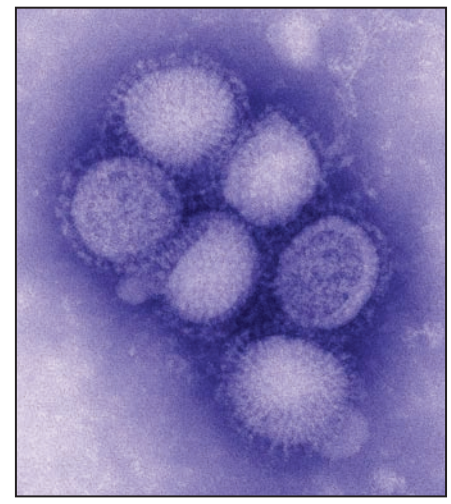
The way Dr. Joseph Kim sees it, the field of influenza vaccine development needs an extreme makeover.

"Every year, three flu strains are selected by the flu experts around the world, which determines which strains the vaccine makers should make and stock for the coming fall," Dr. Kim, president and CEO of San Diego–based Inovio Biomedical Corp., said in an interview. "They can guess right, or they can guess wrong; but every year, you have to change the vaccine. You can't stockpile from the previous year, because the flu strains could change."

Scientists don't accept this approach for most other common vaccines, he noted, including the one for measles, mumps, and rubella. "That doesn't get changed from year to year, but our society has accepted the fact that the one for influenza does," he said. Dr. Kim wants to change that paradigm.

Since 2005, he and his associates at Inovio have been developing DNA-based influenza vaccines capable of providing broad protection against existing as well as newly emerging, unknown seasonal and pandemic influenza strains. To design vaccines, the company developed a process known as SynCon, a way of targeting consensus proteins from multiple strains of H1N1, H2N2, H3N2, and H5N1, "which have collectively caused greater than 90% of all seasonal and pandemic flu events in people in the last 100-plus years," Dr. Kim said. "We felt that those were very good targets."

What separates Inovio's SynCon approach from that of other DNA vaccine manufacturers is that the SynCon vaccines demonstrate potential to protect against new strains of influenza that do not specifically match the vaccine. "So, if the 2009 H1N1 virus mutates, there is no plan B," Dr. Kim said. "There is no backup option; 2009 swine flu could be a big problem or not. No one can predict accurately."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Several companies are developing DNA vaccines against H1N1 flu virus.

Origins of an Alternative

DNA-based influenza vaccines began to draw serious attention about 6 years ago, when infectious diseases experts around the globe expressed concern about a pandemic of H5N1 influenza virus, noted Dr. William Schaffner, chair of the department of preventive medicine at Vanderbilt University, Nashville, Tenn.

"That galvanized the international community," said Dr. Schaffner. "Since that time, the United States government and private capital have gone into research to develop more improved influenza vaccines and to improve the vaccine technology. There has been more research into those areas in the past 5 or 6 years than there has been in the previous 50 years. That's stunning."

The concept of DNA vaccines first emerged in the early 1990s, when researchers discovered that immunizing animals with plasmids—a circular string of DNA that encodes for a specific antigen or vaccine target—generates vaccine responses.

"The beauty of this technology is speed," said Vijay B. Samant, president and CEO of San Diego–based Vical, which develops DNA vaccines. "It's not cell culture. It's not egg-based. It's simple fermentation and two purification steps. It does not require the manufacturer to handle the pathogen. All it needs is a gene sequence; that's good enough for us to make the vaccine.

"Instead of delivering the viruses themselves in some form, you're taking a very simple plasmid, which is a circular string of DNA, and you're putting in a genetic blueprint designed for a specific target, in this case hemagglutinin," Dr. Kim explained. "Once you inject that into muscle cells or skin cells, it uses our own cellular machinery to manufacture those proteins as antigens, and presents them in a customized way. It's like mimicking viral infection without the side effects and replication. DNA vaccines can never replicate. They do not infect; they do not cause disease, ever. There are zero reversion effects."

Delivery Poses Challenges

Until recently, Dr. Kim and other researchers in the field faced a barrier to the advancement of DNA vaccines: inefficient delivery. Delivery methods such as "naked" DNA formulated in water or salt solution, or formulated in lipids or even traditional adjuvants such as aluminum sulfate, and then injected in a syringe were not efficient.

However, a technology developed in the 1990s known as in vivo electroporation is proving to be an effective way to deliver DNA vaccines.

Electroporation works as follows: After a DNA vaccine is injected via syringe into the upper arm or into skin, a short, controlled electrical pulse is delivered directly into that tissue, either from the same needle or from a surrounding needle. This brief pulse of electric current "coaxes the cell membranes to open up their pores," Dr. Kim said. "That brings in the DNA. We remove the electric field and the pores close up. This has been shown in animal species to be effective in up to a 1,000-fold increase in DNA vaccine uptake. The whole procedure takes a couple of seconds."

Not all DNA vaccine manufacturers are using electroporation as a delivery method.

Vical, the first company to produce a vaccine against the pandemic influenza A(H1N1) virus after initial reports of outbreaks in Mexico, uses a patented adjuvant known as Vaxfectin, "which does an amazing job of protecting the DNA before it enters the skeletal muscle cells," Mr. Samant said. "Being a proinflammatory, it attracts the immune system toward the site of the injection to facilitate creation of the right immune response and immune memory."

Mr. Samant noted that the "gentleness" of the Vical vaccination approach, compared with electroporation, allows it to trigger both innate and adaptive immunity. "With that dual response, hopefully that will lead to broader cross protection."

Phase I Trials Begin

On Oct. 1, 2009, the U.S. Navy awarded Vical a $1.25 million contract to support a phase I clinical trial of its vaccine against H1N1 influenza. "Our goal is to get that trial done by later this year," Mr. Samant said.

In a virus challenge and protection study of Inovio's SynCon H1N1 vaccine, mice were injected with the H1N1 virus that caused the 1918 Spanish flu. Mice that received the H1N1 vaccine were completely protected from the virus, whereas all of the unvaccinated animals died within 1 week.

A more recent study of the SynCon H1N1 vaccine tested in ferrets—a model considered to be on par with human influenza—showed that protective antibody responses occurred in 100% of the animals, with a titer of 1:40 or higher. "This is as good as or better than what the matched strains of vaccines have been able to do," Dr. Kim said.

In 2010, the SynCon H5N1 vaccine will undergo human testing in healthy volunteers, followed by tests in combination with the SynCon H1N1 vaccine. Addition of H2N2 and other strains could soon follow.

'Proof Is in the Pudding'

"If we are correct, we can revolutionize how flu vaccines are made and delivered," Dr. Kim said. "Potentially, we can gather enough clinical evidence to show that because you're injecting the same vaccine and generating a memory response, you may not have to take it annually. It could be a booster regimen every few years.

"I cannot predict what the frequencies will be," he added, "but if we can make

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Prep Work Paid Off When H1N1 Emerged in Cities

BY HEIDI SPLETE
Elsevier Global Medical News

The response to the pandemic influenza A(H1N1) virus by the governments and public health officials of Mexico City and New York City in the spring of 2009 reveals successful strategies, but also points to issues that need to be addressed, according to a report published online in the journal Emerging Infectious Diseases.

"In each case, advance planning laid the foundation for enhanced surveillance and a generally effective response, made possible by an extensive public communications campaign and effective political leadership," wrote Dr. David M. Bell of the Centers for Disease Control and Prevention, Atlanta, and his associates.

The researchers summarized the responses of Mexico City and New York City to the H1N1 virus in spring 2009 (Emerg. Infect. Dis. 2009 [doi: 10.3201/eid1512.091232]).

"These megacities may not be representative of cities in low-income countries, which face more daunting problems," the researchers noted.

After the novel H1N1 virus was identified on April 23, 2009, Mexico City followed a pandemic influenza preparedness plan that had been developed for any virus that originated outside Mexico.

Efforts to decrease the spread of the virus included an intense media campaign encouraging people to stay home if they were sick and to avoid close contact such as hugging or kissing in greeting.

"Early in the epidemic, the federal government released antiviral drugs from the national strategic reserve and controlled their distribution," Dr. Bell and his colleagues wrote.

The government successfully introduced a mass media campaign that addressed Mexico City's diverse population and range of literacy rates. In addition, it mobilized private businesses, such as grocery stories and pharmacies, to deliver health messages. The Ministry of Health also used text messages and e-mails to convey public health messages.

The closure of thousands of businesses in Mexico City and throughout Mexico is estimated to have cost the country more than $2.3 billion, and large gatherings such as sporting events were cancelled or postponed, the researchers said.

Despite these costs, the researchers concluded that Mexico City's preparations paid off. "The preexisting pandemic plan and planning process facilitated collaboration, decision making, and rapid development of a communications campaign," they said. But the emergency of the pandemic illustrated several areas in need of improvement, including a limited capacity of laboratories to handle tests and a lack of criteria for reopening schools that closed because of the outbreak.

In New York City, 77% of emergency departments collect electronic information from more than 90% of patient visits. "During spring 2009, these systems were essential for real-time monitoring of the pandemic in NYC," allowing public health officials to track the spread of the virus through the city.

The New York City government kept the public informed during the spring 2009 H1N1 outbreak with press conferences in both English and Spanish, and a government information hotline staffed with live operators answered 98% of calls within 30 seconds, the researchers said. About 50 schools in New York City closed for approximately 1 week.

Unlike Mexico City, New York City did not distribute antiviral drugs from the emergency stockpile because "normal distribution channels sufficed," Dr. Bell and his associates said, but emergency plans called for the distribution of antivirals from the stockpile if necessary.

Decision making based on flu severity in New York City proved challenging given that the case-fatality ratio was unknown. Other challenges included deciding when and whether to close and reopen schools and how to keep children from gathering in groups elsewhere when schools were closed.

In response to the surge in emergency department visits from individuals with flulike symptoms, New York City hospitals were able to plan for additional care sites to handle the expected surge in cases of influenza-like illness in the fall and winter of 2009, the researchers said.

Overall, they concluded that the early responses of Mexico City and New York City to the H1N1 virus outbreak were promising. The problems that did occur would likely have been worse if the disease were more severe or if schools and businesses had remained closed for longer periods, they wrote. ■

Continued from previous page

it longer than 2-3 years, there will also be a dose-savings and a better way of delivering vaccines to people."

One potential pitfall of the DNA vaccine technology is the impending backlash from vaccine naysayers, cautioned Dr. Schaffner.

"We have a hardcore group of vaccine skeptics," he said. "This is a group of people who look askance at vaccines, are dubious about their benefits, and are concerned about how they're manufactured and what's in them. Any innovation, whether it is the addition of an adjuvant, or a new technology such as this, will come to their attention and draw some of their skepticism and opposition. We have to brace for this."

Then there's the fact that DNA influenza vaccines have yet to be studied in rigorous, randomized controlled trials.

"The proof is in the pudding," he said. "The studies have to be done. We await these phase I clinical trials with great interest."

Universal Vaccination Next?

If clinical success is achieved with new influenza vaccines, it could catalyze a significant shift in public health policy, Dr. Schaffner predicted.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has been "inching toward" a recommendation for universal influenza vaccination over the past few years, he noted.

"If you read the current recommendations carefully, we have a quasi-universal recommendation," explained Dr. Schaffner, who is a liaison member of the committee.

"This has drawn manufacturers into the U.S. market, and it further stimulated the rationale and the financing of research into developing and improving influenza vaccine," he said. "This can only be stimulated further by novel H1N1 that's out there now, and by increasing the publicity [about] the kinds of severe illness of healthy people that H1N1 and seasonal influenza illnesses produce.

"I think it will be just a matter of time before we get a universal recommendation," Dr. Schaffner predicted. "An improved vaccine would clearly stimulate such a recommendation."

Dr. Schaffner disclosed that he has been a consultant for various vaccine manufacturers.

He also is a member of a data safety committee for Merck for experimental vaccines. ■

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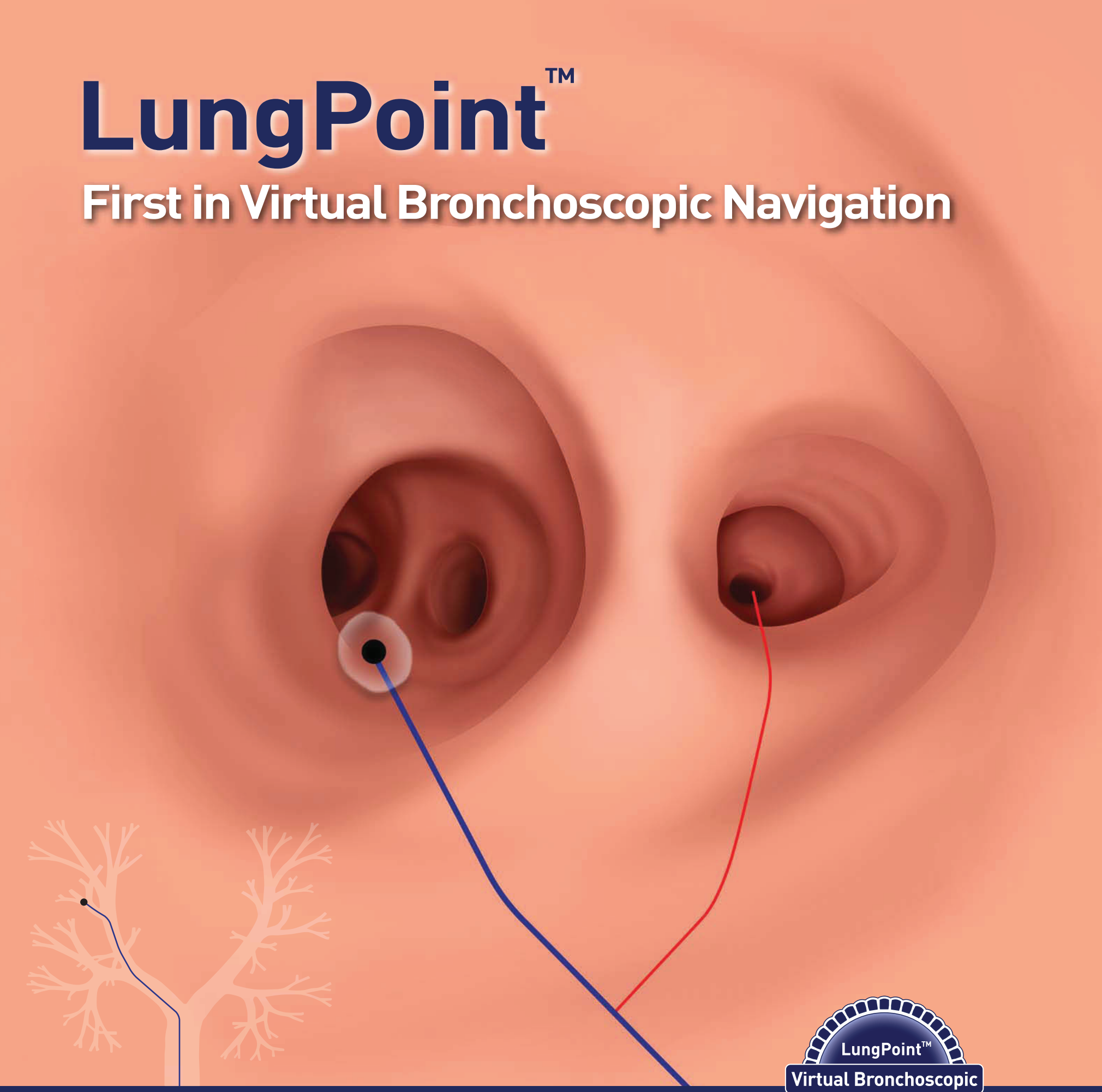

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