Celebrating 10 Years
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Halting smoking boosts LDCT benefits

BY KATIE WAGNER LENNON
Frontline Medical News

Smoking abstinence for 7 years results in a 20% reduction in death from lung cancer – a benefit that is comparable to three rounds of annual screening with low-dose helical computed tomography (LDCT) – in asymptomatic individuals with at least a 30–pack-year smoking history, based on a secondary analysis of 50,263 participants in the National Lung Screening Trial (NLST).

Not smoking for 7 years

See **Abstinence** • *page 6*

Sepsis guidelines ... opening a conversation

The March issue of CHEST Physician featured an article entitled "Sepsis, Septic Shock Redefined by Critical Care Groups." Dr. Steven Q. Simpson, FCCP, has commented in an editorial entitled, "New Sepsis Criteria: A Change We Should Not Make," that can currently be found at *CHEST* Online First at http://journal.publications.chestnet.org/article.aspx?articleid=2499560. This editorial will appear in print in the May issue of *CHEST*. Also, in the May issue, watch for a podcast discussion between Dr. Simpson and one of the authors of the sepsis consensus document, Dr. C. S. Deutschman.

New asthma drug excels in those with sinusitis, polyps

Post hoc analyses of reslizumab trials.

BY BRUCE JANCIN
Frontline Medical News

LOS ANGELES – The newly-approved interleukin-5 inhibitor reslizumab appears to be particularly effective in patients with severe eosinophilic asthma accompanied by chronic sinusitis and nasal polyps, as well as in patients aged 65 and older, based on two separate analyses presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

On March 23, the Food and Drug Administration approved the humanized monoclonal antibody for use with other asthma medicines as maintenance therapy in patients aged 18 years and older with severe asthma.

The post hoc analyses presented at the AAAAI meeting were conducted to highlight the biologic's performance in clinically important but understudied patient subgroups, according to the researchers.

They examined the published 1-year data from the phase III randomized trials that were considered in the drug's approval. For those trials, patients received IV reslizumab at 3.0 mg/kg or placebo every 4 weeks in addition to standard background therapy. The

See **Reslizumab** • *page 4*

INSIDE

Blood test predicts TB progression

BY MARY ANN MOON
Frontline Medical News

An international team of researchers has developed a blood test that identifies the 5%-10% of patients infected with latent tuberculosis who are likely to progress to active TB, up to 18 months before they show any sign of illness, according to a report published in the Lancet.

Worldwide, one-third of the apparently healthy population is infected with *Mycobacterium tuberculosis*, but only a fraction will develop active TB during their lifetimes. Until now there has been no way to predict which of these people will progress and become ill.

Treating all latently infected people in endemic areas for the necessary 6-9 months isn't feasible, but a test that distinguishes which cases will become active would allow targeted preventive therapy. This could potentially interrupt the global spread of TB, said Daniel E. Zak, Ph.D. of the Center

See **Blood test** • *page 10*

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Indication

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

Select Important Safety Information

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

Photosensitivity reaction or rash: Patients treated with Esbriet had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). Patients should avoid or minimize exposure to sunlight (including sunlamps), use a sunblock (SPF 50 or higher), and wear clothing that protects against sun exposure. Patients should avoid concomitant medications that cause photosensitivity. Dosage reduction or discontinuation may be necessary.

Gastrointestinal disorders: Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease, and abdominal pain were more frequently reported in patients treated with Esbriet. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the Esbriet 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the Esbriet 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases.

Adverse reactions: The most common adverse reactions (≥10%) were nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

Drug interactions: Concomitant administration with strong inhibitors of CYP1A2 (eg, fluvoxamine) significantly increases systemic exposure of Esbriet and is not recommended. Discontinue prior to administration of Esbriet. If strong CYP1A2 inhibitors cannot be avoided, dosage reductions of Esbriet are recommended. Monitor for adverse reactions and consider discontinuation of Esbriet as needed.

Start preserving more lung function for patients with IPF[4]

- Esbriet had a significant impact on lung function vs placebo in ASCEND[3,4†]
  - —**48% relative reduction in risk of a meaningful decline in lung function at 52 weeks for patients on Esbriet** vs placebo (17% vs 32%; 15% absolute difference; *P*<0.001)
  - —**2.3× as many patients on Esbriet maintained their baseline function at 52 weeks** vs placebo (23% vs 10% of patients; 13% absolute difference; *P*<0.001)
- Esbriet delayed progression of IPF vs placebo through a sustained impact on lung function decline in ASCEND[3,4†]
  - —**Patients on Esbriet maintained an average of 193 mL more lung function at 52 weeks** vs placebo (–235 mL vs –428 mL; *P*<0.001)
- **No statistically significant difference vs placebo in change in %FVC or decline in FVC volume from baseline to 72 weeks was observed in CAPACITY 006**[3,5]
- Esbriet has been approved outside the US since 2011, with approximately 15,000 patients treated with pirfenidone worldwide[2]

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

ATS=American Thoracic Society; ERS=European Respiratory Society; JRS=Japanese Respiratory Society; ALAT=Latin American Thoracic Association; %FVC=percent predicted forced vital capacity.

*Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.

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

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

Agents that are moderate or strong inhibitors of both CYP1A2 and CYP isoenzymes involved in the metabolism of Esbriet should be avoided during treatment.

The concomitant use of a CYP1A2 inducer may decrease the exposure of Esbriet, and may lead to loss of efficacy. Concomitant use of strong CYP1A2 inducers should be avoided.

Specific populations: Esbriet should be used with caution in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with severe hepatic impairment. Esbriet is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment.

Esbriet should be used with caution in patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of Esbriet as needed. The safety, efficacy, and pharmacokinetics of Esbriet have not been studied in patients with end-stage renal disease requiring dialysis. Use of Esbriet in patients with end-stage renal disease requiring dialysis is not recommended.

Smoking causes decreased exposure to Esbriet, which may alter the efficacy profile of Esbriet. Instruct patients to stop smoking prior to treatment with Esbriet and to avoid smoking when using Esbriet.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of Prescribing Information on adjacent pages for additional Important Safety Information.

References: 1. Raghu G, Rochwerg B, Zhang Y, et al; ATS, ERS, JRS, and ALAT. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med.* 2015;192(2):e3-e19. **2.** Data on file. Genentech, Inc. **3.** Esbriet Prescribing Information. InterMune, Inc. October 2014. **4.** King TE Jr, Bradford WZ, Castro-Bernardini S, et al; for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med.* 2014;371(12):1172]. *N Engl J Med.* 2014;370(22):2083-2092. **5.** Noble PW, Albera C, Bradford WZ, et al; for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet.* 2011;377(9779):1760-1769.

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Esbriet® (pirfenidone) capsules 267 mg

START HERE

Post hoc analyses of benefits

Reslizumab *from page 1*

two trials included close to 1,000 patients aged 12-75 years with baseline blood eosinophil counts of at least 400 cells/mcL and inadequately controlled asthma despite being on at least moderate-dose inhaled corticosteroids. The primary endpoint – frequency of clinical asthma exacerbations – was reduced by 54% with reslizumab compared to placebo (Lancet Respir Med. 2015 May;3[5]:355-66).

For the first post hoc analysis, Dr. Steven F. Weinstein compared 52-week outcomes in 250 patients with chronic sinusitis, including 150 who also had nasal polyps, in juxtaposition to the total two-study population of 953 eosinophilic asthma patients. Of note, aspirin sensitivity was present in 37% of those with chronic sinusitis and nasal polyps (CSwNP) compared to 11% of total participants. The CSwNP group had higher blood eosinophil levels, too: an average of 884 cells/mcL, compared with 655/mcL in the study population as a whole.

The frequency of clinical asthma

Esbriet® (pirfenidone) capsules 267 mg

Rx only

BRIEF SUMMARY

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

Increases in ALT and AST >3 × ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration sections 2.1 and 2.3 in full Prescribing Information]*.

5.2 Photosensitivity Reaction or Rash

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

5.3 Gastrointestinal Disorders

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

6 ADVERSE REACTIONS

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

- Liver Enzyme Elevations *[see Warnings and Precautions (5.1)]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Disorders *[see Warnings and Precautions (5.3)]*

ESBRIET® (pirfenidone)

6.1 Clinical Trials Experience

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience

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

Blood and Lymphatic System Disorders
Agranulocytosis

Immune System Disorders
Angioedema

Hepatobiliary Disorders
Bilirubin increased in combination with increases of ALT and AST

exacerbations was 3.22 episodes in 52 weeks in CSwNP patients on placebo and 0.56 in those given reslizumab, for an 83% reduction in the active treatment arm. In the overall study population, the frequency was 1.81 episodes with placebo versus 0.84 with reslizumab, for a less robust but still significant 54% reduction.

Among all subjects with chronic sinusitis who received reslizumab, the reduction in exacerbations was intermediate at 70%, with 2.81 episodes in controls and 0.83 episodes with reslizumab.

Clinical asthma exacerbations were defined as the use of systemic steroids by patients not already on such medication or at least a twofold increase in doses of inhaled or systemic corticosteroids for at least 3 days.

The placebo-subtracted improvement in lung function from baseline to 52 weeks in reslizumab-treated patients was 326 mL in the CSwNP group, 235 mL in all patients with chronic sinusitis, and 109 mL in the overall study population, according to Dr. Weinstein, an allergist-immunologist practicing in Huntington Beach, Calif.


DR. WEINSTEIN

A 0.5-point improvement on the validated Asthma Quality of Life Questionnaire (AQLQ) is accepted by researchers as the minimum for demonstrating clinically significant benefit. The 52-week placebo-subtracted improvement on this measure was 0.69 points in the reslizumab-treated CSwNP group, 0.47 in the total cohort of asthmatics with chronic sinusitis, and 0.27 points in the overall reslizumab-treated population.

Similarly, the average placebo-subtracted improvement on the Asthma Control Questionnaire–6 was 1.45 points in reslizumab-treated patients with CSwNP, a sixfold greater response than seen in the total study population, Dr. Weinstein noted.

A similar pattern of greater-than-average efficacy with reslizumab on both primary and secondary study endpoints was seen in the 77 patients aged 65 years and older as compared with those aged 18-64 years, according to Dr. David Bernstein, professor of medicine and environmental health at the University of Cincinnati.


DR. BERNSTEIN

Older patients made up only a small fraction of total subjects in the two trials, yet asthma affects an estimated 7% of Americans age 65 and up, and rates of asthma hospitalization and mortality are higher than in younger patients, he noted. With reslizumab, the older cohort had a 67% reduction in the frequency of asthma exacerbations, while the younger patients had a 53% reduction.

Measures on the AQLQ, the Asthma Control Questionnaire–7, and the Asthma Symptom Utility Index were consistently better in older as compared to younger reslizumab-treated patients. Only the older group had minimal clinically significant improvements in all three measures.

The two post hoc analyses were funded by Teva Pharmaceuticals. Both investigators serve on advisory boards for Teva and multiple other pharmaceutical companies.

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ESBRIET® (pirfenidone)

7 DRUG INTERACTIONS

7.1 CYP1A2 Inhibitors

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

Strong CYP1A2 Inhibitors

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

Moderate CYP1A2 Inhibitors

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

Concomitant CYP1A2 and other CYP Inhibitors

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

7.2 CYP1A2 Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: **Pregnancy Category C.**

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

ESBRIET® (pirfenidone)

8.6 Hepatic Impairment

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

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

8.7 Renal Impairment

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

8.8 Smokers

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

10 OVERDOSAGE

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

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

17 PATIENT COUNSELING INFORMATION

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

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions (5.1)]*.

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required *[see Warnings and Precautions (5.3)]*.

Smokers

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

Take with Food

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

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Smoking, LDCT

Abstinence *from page 1*

plus screening for lung cancer with LDCT conferred an additional 10% reduction in lung cancer mortality. Similar patterns for smoking cessation benefits were noted for overall mortality, as well.

"This study is the first to quantify the benefit of smoking cessation coupled with lung cancer screening in a cohort that is asymptomatic," wrote Dr. Nichole T. Tanner of the Medical University of South Carolina, Charleston, and her colleagues (Am J Respir Crit Care. 2016 March 1. doi: 10.1164/rccm.201507-1420OC). "[Its] findings highlight the importance of integrating smoking cessation efforts into lung cancer screening programs."

The NLST subset study included 47,902 participants who self-identified as non-Hispanic white and 2,361 who self-identified as non-Hispanic black; 24,190 were current smokers and 26,073 were former smokers who had quit within the 15 years prior to entering the study.

Participants ranged in age from 55 to 74 years at the time of randomization and had a 30–pack-year or more history of cigarette smoking.

All participants were screened for lung cancer with either LDCT or a chest radiograph examination.

A 20% reduction in death from lung cancer was seen in those who had abstained from smoking for 7 years and were screened for lung cancer with a chest radiograph and in those who had undergone three rounds of annual screening for lung cancer with LDCT and continued to smoke.

For former smokers screened with LDCT, the risk of dying of lung cancer decreased at a faster rate than it did for those screened with chest radiographs.

For each additional year an individual abstained from smoking and had an LDCT screen, the risk of dying of lung cancer decreased by 9%.

For those individuals who abstained from smoking and had been screened with a chest x-ray, the risk of dying of lung cancer decreased by 3%.

In contrast, lung cancer mortality increased by 10% for each 10 pack-years smoked for those screened with LDCT (HR, 1.10; 95% CI, 1.08-1.13).

In both screening groups, "an additional 6% risk of death from all causes (was seen) for each additional 10 pack-years smoked."

In addition, black study participants who had quit smoking at trial entry had "a more pronounced benefit" from having done so, compared with the white study participants (HR, 0.53, 95% CI, 0.28-1.0).

Dr. Tanner, one of this secondary analysis's authors reported receiving grants from ACCP OneBreath Foundation and from Olympus America, Cook, and the American Cancer Society for other work.

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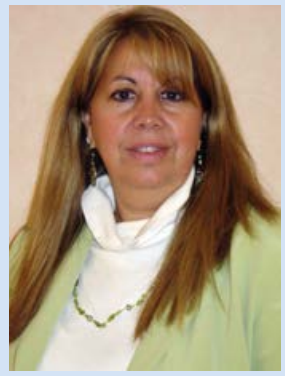
IN THIS ISSUE



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

VIEW ON THE NEWS

Smoking cessation paramount

This secondary analysis was limited by the fact that the National Lung Screening Trial does not have information about smoking cessation or persistence during the trial.

The finding of black former smokers having a hazard rate for lung cancer mortality of 0.53, compared with white former smokers, was reassuring because there is evidence that African Americans are at higher risk for lung cancer at lower smoking intensities than whites.

While this secondary analysis suggests that screening for lung cancer can reduce lung cancer death risk, lung cancer screening alone is not adequate for preventing the disease.

Screening must be linked to smoking cessation efforts in those who are current smokers and may need to follow criteria that are different from those used in the NLST.

Implementation of lung cancer screening will be a serious challenge that must be linked to smoking cessation efforts in those who are current smokers at the time they enter a screening program, both for Centers for Medicare & Medicaid Services reimbursement and for medical appropriateness.

Dr. Christine D. Berg is with Johns Hopkins Medicine, Baltimore, and the division of cancer epidemiology and prevention at the National Cancer Institute, Bethesda, Md. She made these remarks in an editorial accompanying Dr. Tanner's report (J Respir Crit Care. 2016 March 1. doi: 10.1164/rccm.201511-2270ED). She reported receiving personal fees from Medial CS, and she was the study director of the NLST.

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Cold turkey better for smoking cessation

BY MARY ANN MOON
Frontline Medical News

Quitting smoking abruptly leads to higher abstinence rates both at 4 weeks and 6 months, according to a report published online in the Annals of Internal Medicine.

Worldwide guidelines for smoking cessation generally recommend abrupt cessation over a gradual reduction in smoking, based on data from observational studies. However a recent review of 10 randomized trials concluded that quitting "cold turkey" produces only slightly higher quit rates, said Nicola Lindson-Hawley, Ph.D., of the department of primary care health services, University of Oxford (England), and her associates.

They compared the two approaches in a noninferiority trial involving 697 adults treated at 31 primary care practices in England during a 2.5-year period. The study participants smoked at least 15 cigarettes per day and had an end-expiratory carbon monoxide concentration of at least 15 parts per million.

The average age was 49 years, and the study population was evenly divided between men and women. Their mean score on the Fagerström Test for Cigarette Dependence was 6, indicating a high degree of dependence.

These participants were randomly assigned either to stop smoking abruptly on a quit date 2 weeks from baseline (355 patients) or to stop gradually, by reducing their cigarette use by half at 1 week from baseline, by half again during the second week, and completely by a quit date 2 weeks from baseline. The latter group was given a choice of three structured reduction programs to follow before the quit date, as well as nicotine patches and a choice of short-acting nicotine replacement products (gum, lozenges, nasal sprays, sublingual tablets, inhalators, or mouth sprays). The abrupt-cessation group received only the nicotine patches just before the quit day. Both groups received identical behavioral counseling, nicotine patches, and nicotine replacement products after the quit date.

The primary outcome measure, abstinence at 4 weeks, was achieved by 49% of the abrupt-cessation group, compared with only 39.2% of the gradual-cessation group (relative risk, 0.80). Thus, gradual cessation did not prove to be noninferior to abrupt cessation. The secondary outcome measure of abstinence at 6 months also was superior for the abrupt-cessation group (22%) over the gradual-cessation group (15.5%), Dr. Lindson-Hawley and her associates reported (Ann Intern Med. 2016 Mar 15. doi: 10.7326/M14-2805).

Most of the between-group difference was attributed to the fact that fewer participants in the gradual-cessation group actually attempted to quit on their quit date (61.4% vs. 71.0%). Relapse rates were similar between the two study groups at 4 weeks (36.2% vs. 31.0%) and at 6 months (74.8% vs. 69.1%).

"These results imply that, in clinical practice, we should encourage persons to stop smoking abruptly and not gradually," Dr. Lindson-Hawley and her associates wrote. "However, gradual cessation programs could still be worthwhile if they increase the number of persons who try to quit or take up support and medication while trying."

The study was supported by the British Heart Foundation, Cancer Research United Kingdom, the Economic and Social Research Council, the Medical Research Council, and the National Institute for Health Research. Dr. Lindson-Hawley reported having no relevant financial disclosures; two of her associates reported ties to Pfizer, GlaxoSmithKline, and McNeil.

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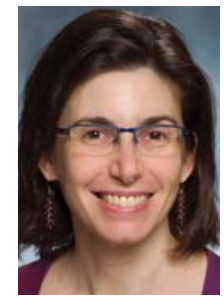
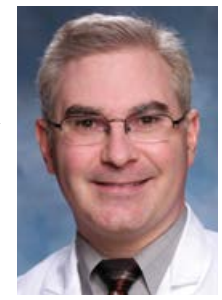
VIEW ON THE NEWS

Don't abandon gradual quitting yet





The trial by Nicola Lindson-Hawley, Ph.D., is well designed and suggests that setting a quit date and quitting abruptly increases long-term cessation rates in smokers who want to quit. However, a gradual approach to smoking cessation still may be useful for some smokers, so that method shouldn't be entirely abandoned just yet.

Many smokers try several times to quit abruptly but are not successful. They may not wish to set another abrupt quit date for fear of "failing" yet again. However, they may instead respond well to gradually reducing their smoking, with the eventual goal of reducing it all the way to zero.

These findings raise important questions about how clinicians should approach patients who smoke and are ready to quit.

Dr. Gabriela S. Ferreira and Dr. Michael B. Steinberg are at the Robert Wood Johnson Medical School in New Brunswick. Dr. Ferreira reported having no relevant financial disclosures; Dr. Steinberg reported receiving personal fees from Arena Pharmaceuticals, Major League Baseball, and Pfizer outside of this work. Their remarks (Ann Intern Med. 2016 Mar 15. doi: 10.7326/M16-0362) appeared in an editorial that accompanied Dr. Lindson-Hawley's report.

COPD with asthma more costly than COPD alone

BY RICHARD FRANKI
Frontline Medical News

Health care costs almost $400 more per year for patients with chronic obstructive pulmonary disease who have a history of asthma, based on records of over 45,000 adults in British Columbia, reported Dr. Mohsen Sadatsafavi of the University of British Columbia, Vancouver, and his associates (Ann Am Thorac Soc. 2016 Feb;13[2]:188-96).

The largest component of that excess was medication costs. These excesses were somewhat offset by hospitalization costs, which were $196 less per year for the COPD + asthma group, the investigators said.

Inhaled corticosteroids/long-acting beta-agonists cost almost $178 more per year for the COPD + asthma patients. Inhaled corticosteroids were next, with a cost excess of $64 annually, followed by long-acting muscarinic agents ($59), short-acting beta-agonists ($46) and leukotriene receptor agonists ($19).

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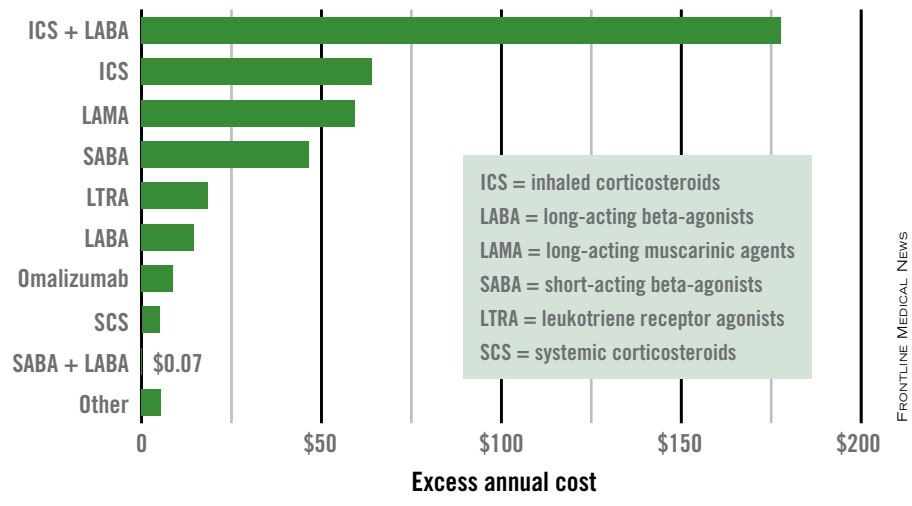
Excess annual drug costs for COPD + asthma vs. COPD alone



Note: Based on data for 22,565 subjects in each of the two groups (COPD, COPD + asthma).
Source: Ann Am Thorac Soc. 2016 Feb;13(2):188-96

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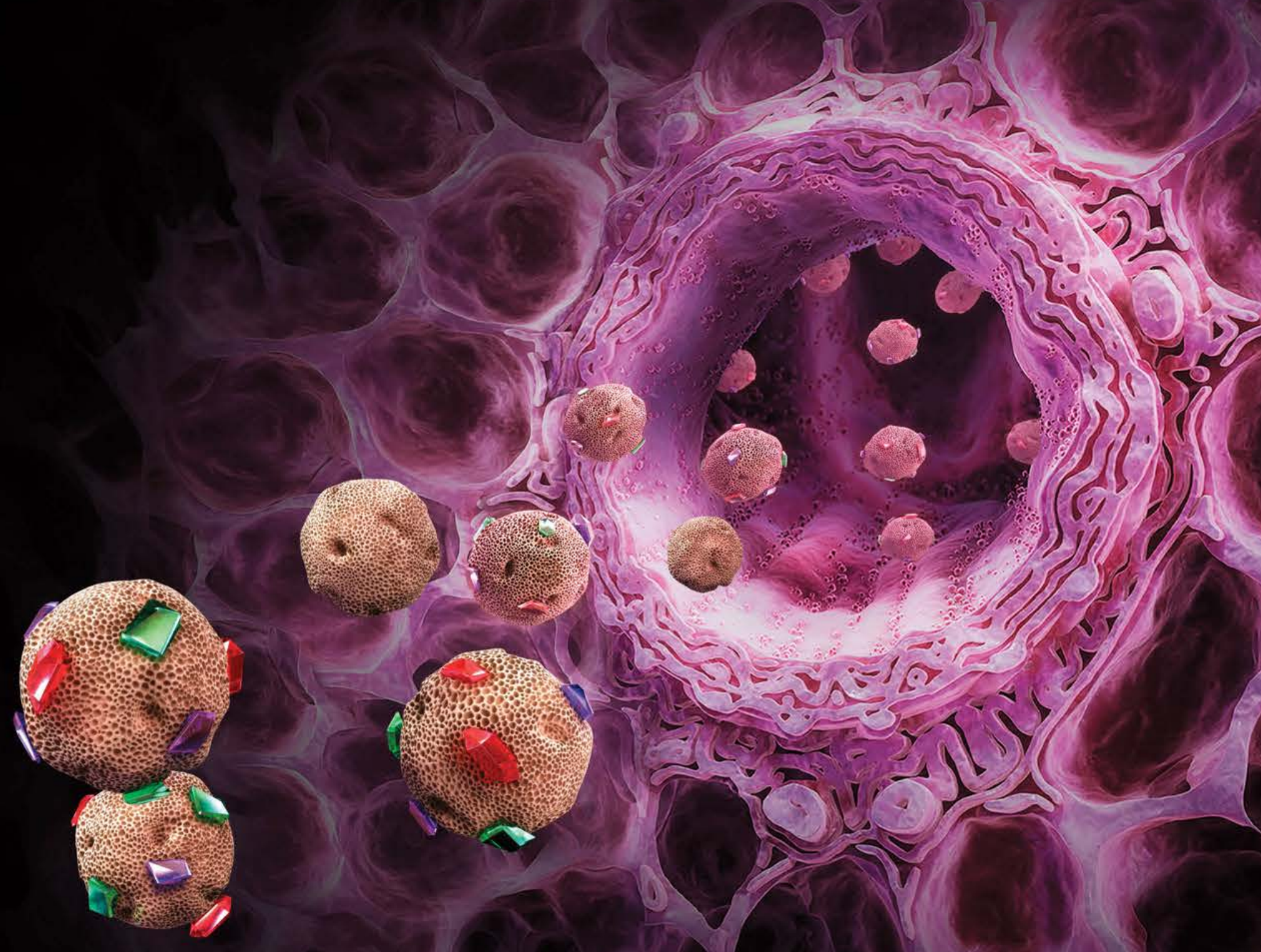

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Possibly useful for monitoring treatment

Blood test *from page 1*

for Infectious Disease Research, Seattle, and his associates.

Such a test also might be used to assess treatment response, as well as to enroll only the highest-risk carriers of *M. tuberculosis* in trials of new drugs and vaccines, they added.

The investigators began by analyzing gene expression in peripheral whole-blood samples from 6,363 apparently healthy adolescents participating in a South African cohort study who were followed for 2-4 years for the development of active TB. They compared RNA-sequencing data from 46 participants who developed active TB against that from 107 matched control subjects who remained healthy and identified a candidate 16-gene risk signature for TB progression.

"Robust discrimination between progressors and controls based on the expression of the gene pairs in the signature was readily apparent," the researchers said.

In this subgroup of patients, the risk signature had a 71.2% sensitivity for predicting active TB during the 6 months preceding diagnosis, a 62.9% sensitivity during the 12 months preceding diagnosis, and a 47.7% sensitivity during the 18 months preceding diagnosis.

The specificity was 80.6%.

To validate their findings, the investigators adapted the risk signature to a more practical PCR platform and used it to predict the risk of active TB in the remainder of the study population. The risk signature remained comparably sensitive and specific in this analysis.

To validate their findings in an independent cohort, Dr. Zak and his associates analyzed whole-blood samples from 4,466 apparently healthy adults from South Africa and the Gambia who were participating in a study of household contacts of patients with newly diagnosed active TB.

Continued on following page

VIEW ON THE NEWS

Potential to transform TB control worldwide

The current TB epidemic is sustained by the emergence of new cases from the 2 billion people worldwide who have latent TB infection, and from the subsequent infection of their contacts. A test that identifies which people with latent infection will progress to active infection would transform TB control by allowing targeted treatment that would prevent these new cases from emerging.

Another significant finding from the work of Dr. Zak and his associates is that differences in gene expression were detected months before TB symptoms developed. This suggests that progressors have an immune response well before they are diagnosed, that their immune response differs from that of people who remain well, and that the progression from latent to active TB infection is a continuum in the battle between host and pathogen.

Dr. Michael Levin and Dr. Myrsini Kaforou are in the section for pediatric infectious diseases at Imperial College London. They reported being members of an EU-funded TB vaccine consortium and previously worked on an EU-funded study of TB biomarkers, both of which included some of Dr. Zak's associates. Dr. Levin and Dr. Kaforou made these remarks in an editorial comment accompanying Dr. Zak's report (Lancet. 2016 Mar 23. doi: 10.1016/S50140-6736[16]00165-3).

Trial finds fluticasone-salmeterol inhalers to be safe

BY M. ALEXANDER OTTO
Frontline Medical News

LOS ANGELES – Fluticasone-salmeterol inhalers (Advair) are as safe as and more effective than fluticasone monotherapy inhalers are for patients with moderate to severe asthma, according to a randomized trial from its drug maker, GlaxoSmithKline, presented at the annual meeting of the American Academy of Allergy, Asthma and Immunology and simultaneously published online in the New England Journal of Medicine.

The study is the first of several that the Food and Drug Administration required from Glaxo and other manufacturers in 2010 to evaluate the safety of long-acting beta-2 agonists (LABAs) such as salmeterol when used in combination with inhaled corticosteroids, after it became clear that LABAs, when used alone, increase the risk of serious asthma complications, including death (N Engl J Med. 2016 Mar 6; doi:1 0.1056/NEJMoa1511049).

Current black box warnings on fluticasone-salmeterol (Advair), Merck's mometasone-formoterol inhaler (Dulera), and AstraZeneca's budesonide-formoterol combo (Symbicort)note that data are "inadequate to determine" if concomitant steroids mitigate the risk of LABAs..

Merck and AstraZeneca's studies are ongoing.

"This is the first really large study to show a decrease in exacerbations with [fluticasone-salmeterol]," principal investigator Dr. David Stempel, with Glaxo's Respiratory Clinical Development program in Durham, N.C., said at the meeting.

However, because "patients with a history of life-threatening or unstable asthma" – including those who, at any point, had been intubated for asthma – "were excluded from the study, our results cannot be extrapolated to such patients," the researchers wrote.

Adults and adolescents at least 12 years old, with a history of severe asthma exacerbations requiring the use of inhaled glucocorticoids or hospitalization in the previous year, but not in the month before enrollment, were included.

There were 5,834 subjects randomized to fluticasone-salmeterol and 5,845 to fluticasone alone, both for 26 weeks.

Adherence to the study medications was 95%.

There were 36 serious asthma-related events – endotracheal intubation or hospitalization – in 34 patients (0.58%) in the fluticasone-salmeterol group, and 38 events in 33 patients (0.56%) in the fluticasone-only group.

While 480 fluticasone-salmeterol patients (8%) had at least one severe asthma exacerbation, at least one severe exacerbation occurred in 597 fluticasone-only patients (10%).

The work was funded by GlaxoSmithKline, and the authors are current or former employees.

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VIEW ON THE NEWS

Highest risk patients excluded

At first glance, these results appear to be reassuring. However, patients were excluded from the trial if they had a history of life-threatening or unstable asthma. Thus, it is not surprising that only two patients in the trial had life-threatening asthma and that adherence to study medication was 95%, a rate unheard of in clinical practice.

What practical conclusions can be drawn from this study? It is clear that among patients with asthma who have not had life-threatening episodes in the past and are highly adherent to their drug regimen, it is likely that salmeterol together with fluticasone in a single inhaler is safe. For these patients and this combination, the black-box warning should be lifted. This is an important result, and it stresses that most patients with asthma, and especially those without serious episodes, can reach high levels of symptom control and avoid frequent exacerbations by simply using their inhalers every day.

What remains unanswered is whether this conclusion applies to patients who have the most severe and unstable disease, since these are the patients for whom guidelines still recommend the use of LABAs [long-acting beta-2 agonists], combined with inhaled glucocorticoids, as first-line treatment. For these patients, the safe clinical approach is to maintain the same precautions in using fluticasone-salmeterol that have been recommended until now for all patients with asthma.

Dr. Fernando Martinez is a professor of pediatrics and director of the Asthma/Airway Disease Research Center at the University of Arizona, Tucson. He made his comments in an editorial (N Engl J Med. 2016 Mar 2016. doi: 10.1056/NEJMe1601040).

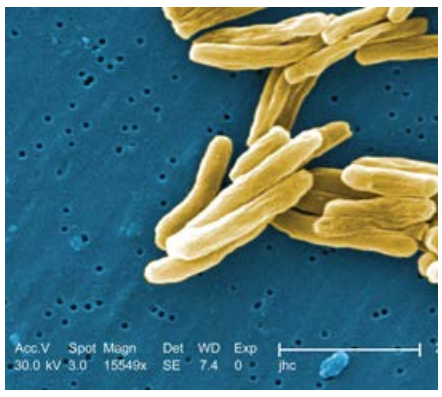
Continued from previous page

During follow-up, 43 progressors and 172 control subjects were identified at the South African study site, and 30 progressors and 129 control subjects were identified at the Gambian study site.

The risk signature again reliably distinguished patients who progressed from latent to active TB from those who didn't progress, months before any sign of illness surfaced.

"When applied to combined data from 4 studies of HIV-uninfected South African adults involving 130 prevalent TB cases and 230 controls, the signature discriminated between patients with active TB and controls with 87% sensitivity and 97% specificity," the investigators noted.

Adapting the risk signature further to microarrays so that it could be used in other datasets, the researchers found that it readily distinguished latent from active TB infection in stored samples from more cohorts from the United Kingdom, South Africa, and Malawi. In these cases the risk signature also distinguished active TB from other pulmonary diseases and from other diseases of childhood, and did so regardless of whether the study subjects were coinfected with HIV or not.



CDC/Janice Carr

"Finally, applying the signature to data from a treatment study showed that the active TB signature gradually disappears during 6 months of therapy," Dr. Zak and his associates wrote (Lancet 2016 March 23. doi:10.1016/S0140-6736[15]01316-1).

These latter observations suggest that the risk signature may reflect the TB bacterial load in the lung.

The study results were particularly encouraging given the marked diversity among these study populations.

The participants had different age ranges, different infection or exposure status, distinct ethnic and genetic backgrounds, different local epidemiology, and different circulating strains of *M. tuberculosis*. "Our results … pave the way for the establishment of diagnostic methods that are scalable and inexpensive.

Our results … pave the way for the establishment of diagnostic methods that are scalable and inexpensive.

An important first step would be to test whether the signature can predict TB in the general population, rather than the select populations included in this project," the investigators added.

This study was funded by the Bill and Melinda Gates Foundation, the National Institutes of Health, the European Union, the South African Medical Research Council, and Aeras. The researchers reported having no relevant financial disclosures.

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PULMONARY PERSPECTIVES®: Three lung function tests in preschoolers

BY DR. PELTON A. PHINIZY AND DR. STEPHANIE LOVINSKY-DESIR

Pediatricians are often taught that children are not simply small adults. Unique aspects of normal lung development and respiratory pathology in small children require clinicians and researchers to appreciate the applicability and utility of pulmonary function testing modalities that were originally designed for adults. Evaluation of lung function in preschool children (ages 3 to 5 years)

DR. PHINIZY

DR. LOVINSKY-DESIR

can be especially important for clinical assessment, tracking disease progression, and judging utility/effectiveness of medication for many respiratory disorders (eg, wheeze, chronic lung disease of prematurity, and cystic fibrosis). However, testing in this particular age group has certain technical challenges specific to the maneuver required for each test. In addition, young children can have short attention spans and, thus, need to be supported and engaged throughout the testing maneuver. Here, we review three methods of assessing pulmonary function: spirometry, impulse oscillometry (IOS), and fractional exhaled nitric oxide (FeNO); with emphasis on the advantages, disadvantages, and applicability in preschool children.

Spirometry

Spirometry is the most widely used method of measuring pulmonary function, and reliable results can be obtained in many preschool children. The maneuver requires active participation as the child inhales to total lung capacity and exhales rapidly and forcefully to residual volume. The forced vital capacity and forced expiratory volume in the first 1 second (FEV_1), among other values generated from the study, are then compared either to reference values or to previous results from the same child. However, preschool children are frequently unable to exhale forcefully for greater than a few seconds (6 seconds is recommended). Thus, the FEV in 0.5 seconds ($FEV_{0.5}$) or 0.75 seconds ($FEV_{0.75}$) is often used instead of the FEV_1 as an indicator of airflow limitation. In order to overcome potential difficulties with performing acceptable and reproducible maneuvers, incentives are built into the software to encourage maximal effort.

Performing spirometry pre- and post-bronchodilator treatment can be helpful in identifying a reversible component to lower airway obstruction in the wheezy preschool child. In addition, these studies can be particularly helpful in the premature child to help distinguish fixed vs. reversible lower airway obstruction. However, it has been suggested that spirometry may not be sensitive enough in some milder cases of wheezing to detect obstruction (Marotta et al. *J Allergy Clin Immunol.* 2003;112[2]:317). Spirometry is also very useful in children with cystic fibrosis. Reductions in air flow can support the decision for treatment with antibiotics in a child who might not be able to clearly articulate symptoms of an acute exacerbation.

Several portable spirometry devices are now readily available for use in both the clinical and research settings. Furthermore, normative reference values exist within this age group allowing for longitudinal assessments of lung function and growth in comparison to healthy populations; albeit, reference values are not well validated for some subpopulations of races/ethnicities.

Impulse Oscillometry (IOS)

IOS is a noninvasive method for measuring the impedance of flow in the respiratory system. Sound waves are generated by a loudspeaker and flow via a mouthpiece through the airways while the child is spontaneously tidal breathing. The respiratory system resistance (frictional losses) and reactance (elasticity) are then calculated from the resulting signal. IOS is often referred to as "effort-independent" and is generally perceived to be easier for preschool children because there is minimal active participation required. However, in order to obtain acceptable results, the child should perform a minimum of three trials, 30 to 45 seconds each, in a relaxed state. One recent study in a longitudinal birth cohort of over 400 children reported fewer acceptable trials with IOS compared with spirometry in 3- to 5-year-olds (Kattan et al. *Am Thorac Soc Conf Abstract*; 2013:A3695). Unacceptable trials may result from swallowing, vocalizing, breath holding, or air leaks.

While spirometry is a classic test used to determine change in airway obstruction in response to bronchodilators, IOS may be more sensitive in detecting small changes in airway resistance or lung compliance. In fact, IOS is thought to be more sensitive to signs of improvement in asthma following initiation of controller medications that may not be ascertainable by spirometry (Guilbert et al. *N Engl J Med*. 2006;354[19]:1985). Also, during methacholine challenge testing, IOS can detect increases in resistance at lower doses and earlier than changes in FEV1 (Schulze et al. *Respir Med*. 2012;106[5]:627). Thus, in addition to its clinical applicability, IOS might be a more sensitive tool in research settings, for example, in identifying acute or chronic airway changes in response to environmental exposures.

The device for measuring IOS can be relatively compact and lightweight consisting of a box for the hardware and an arm support for the mouth piece; however, it does require connection to a computer. Additionally, reference values for IOS are limited, and normative values need to be established to account for potential differences by sex, age, and height.

Fractional Exhaled Nitric Oxide

FeNO is another tool for assessment of respiratory disease in young children, particularly in the evaluation of allergic airway disease, such as asthma. This noninvasive test measures the amount of endogenously produced nitric oxide in the airway, the majority of which is produced by epithelial and inflammatory cells in chronic airway inflammation. For adults, quality standards require inhalation to total lung capacity and then exhalation against a backpressure of 5 cm H_2O at a rate of 50 mL/s for 10 seconds. Recent work suggests that young children may not need to exhale for a full 10 seconds to reach a steady state level of exhaled NO adequate for measurement because of their smaller lung volumes. Shorter times of 6 seconds have been suggested and are being validated (Heijkenskjöld-Rentzhog et al. *Pediatr Allergy Immunol.* 2015;26[7]:662).

FeNO may be a more sensitive test for identifying airway inflammation associated with mild asthma compared with spirometry. A recent study in 5- to 6-year-old children demonstrated that FeNO was significantly associated with both the presence of wheeze and airway hyperreactivity, whereas spirometry and IOS were not (Lee et al. J Asthma. 2015;52[10]:1054). However, there are limited data to support the utility of FeNO in assessing response to treatment. A Cochrane review reported no clear benefit when FeNO was compared with the use of clinical symptoms and spirometry to help guide chron-

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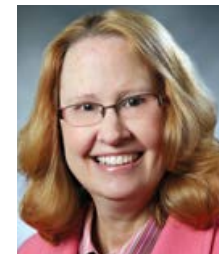
VIEW ON THE NEWS



Dr. Susan Millard, FCCP, comments: Every day in pulmonary clinic, parents of toddlers and preschoolers state that they were told "asthma can only be diagnosed with pulmonary function testing." This supposition is not true, yet, there are so many situations in which it would be helpful! This article by Drs. Phinity and Lovinsky-Desir from Columbia University Medical Center highlights aspects of pulmonary function testing in these often uncooperative, inattentive little patients.

There are other important articles for the interested reader. A great resource is the American Thoracic Society and European Respiratory Society statement regarding Pulmonary Function Testing in Preschool Children (*Am J Respir Crit Care Med.* 2007;175[12]:1304-1345). It is a comprehensive review of spirometry, tidal breathing measurement, the interrupter technique, the forced oscillation technique, and the multiple-breath inert gas washout technique. Dr. Eigen, from Indiana University, has published the sentinel article on spirometry in preschool children (Eigen H, Bieler H, Grant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med.* 2001;163[3 Pt1]:619-623).

Exhaled nitric oxide testing is also highlighted in this article. The applications for this type of testing are certainly more controversial in all age groups but at the present time with the available commercial equipment, it is not a technique commonly used in preschoolers. The technique requires exhalation at a continuous flow rate to measure this biomarker. Our laboratory tests FeNO in children age 7 and above. Finally, Singer's study, cited in this article, requires reproducing and expansion to substantiate that FeNO may identify children at risk for later asthma.

Isavuconazole equivalent to voriconazole for aspergillosis

BY CHRISTINE KILGORE
Frontline Medical News

The broad-spectrum triazole isavuconazole was as effective as voriconazole in patients with suspected invasive mold disease and caused significantly fewer drug-related adverse events, particularly those of the skin, eyes, and hepatobiliary system, a randomized double-blind study of 516 adults has shown.

The newer agent "could allow safer therapy" for the primary treatment of invasive aspergillosis and other mold disease than standard therapy with voriconazole, researchers for the industry-sponsored SECURE trial say in a report in the Lancet.

The researchers assessed the safety and efficacy of isavuconazole versus voriconazole in patients with invasive mold infection. Patients were recruit-

Continued on following page

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ic therapy in children with asthma (Petsky et al. Cochrane Database Syst Rev. 2009;[4]:CD006340). Yet, FeNO is increasingly used to detect patients who have current wheeze and predict future asthma (Singer et al. *Allergy.* 2013;68[4]:531). Thus, FeNO might be the better choice for detecting small amounts of increased airway inflammation in preschool children who may eventually develop asthma.

There are two types of analyzers for FeNO. The first, a chemiluminescence analyzer, provides high quality data but is more expensive, difficult to transport, and more often used in research settings. The second, an electrochemical sensor device, is less expensive and more easily portable but has limited sensitivity compared with the chemiluminescence analyzers. Similar to spirometry, visual incentive programs have been developed to assist with subject cooperation. Nonetheless, even with shorter exhalation cutoff times and incentive programs, young children may have difficulty with the maneuver.

While we have reviewed three of the most commonly used and feasible pulmonary function testing methods used today in preschool children, there are several other modalities available for this young population. Other tests include the interrupter technique, tidal breathing analysis, and the lung clearance index. These tests also have advantages and disadvantages. Ultimately, there is no "best test" for all situations, and a test is only as good as the question being asked. It must also be emphasized that proper training of the person conducting the study is critical for all methods of measuring pulmonary function. Despite potential challenges in this young age group, pulmonary function testing can be both practical and useful in the diagnosis and management of respiratory conditions in preschool children.

Dr. Phinizy and Dr. Lovinsky-Desir are from the Division of Pediatric Pulmonology, Department of Pediatrics, Columbia University Medical Center, New York, NY.

Learn more about OFEV inside.

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Elevated Liver Enzymes

- OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.
- OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN.
- Conduct liver function tests prior to treatment, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Monitor for adverse reactions and consider dosage modifications, interruption, or discontinuation as necessary for liver enzyme elevations.

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

*This conditional recommendation means that clinicians are encouraged to discuss preferences with their patients when making treatment decisions as the majority of patients would want treatment, but many would not.[1]

ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; ERS, European Respiratory Society; FVC, forced vital capacity; JRS, Japanese Respiratory Society.

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Continued from previous page

ed from 102 centers across 26 countries over a 7-year period and were randomized to receive either drug.

In the study group of 516 adults with suspected invasive mold infection who received at least one dose of either drug, isavuconazole was noninferior to voriconazole, based on all-cause mortality at 6 weeks.

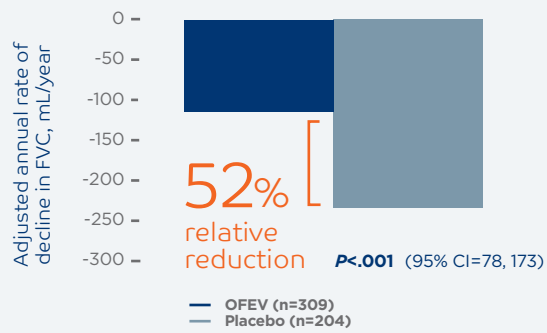
All-cause mortality at 6 weeks in this intention-to-treat group, of whom more than 80% had hematologic malignant disease, was 19% in the isavuconazole group and 20% in the voriconazole group. All-cause mortality "provides the most objective and reproducible effect of therapy, and approximates best the attributable mortality, because deaths due to competing causes occur increasingly after 6 weeks," Dr. Johan A. Maertens of the UZ Leuven (Belgium), and his associates wrote. Secondary endpoints included overall response among patients found by an independent review committee to have proven or probable invasive mold disease – the study's modified intention-to-treat population – as well as all-cause mortality at days 42 and 84.

All-cause mortality in this modified intention-to-treat group, as well as in patients found to have

The totality of the evidence demonstrates that OFEV slows IPF progression[2-6]

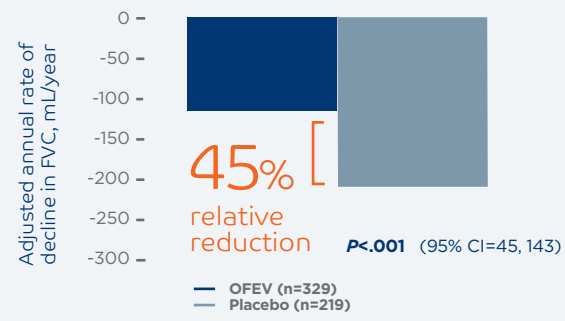
REPRODUCIBLE REDUCTIONS IN THE ANNUAL RATE OF FVC DECLINE ACROSS 3 TRIALS[2]*

INPULSIS®-1 (Study 2)[2,7]



- -115 mL/year for OFEV (nintedanib) compared with -240 mL/year for placebo*

INPULSIS®-2 (Study 3)[2,7]



- -114 mL/year for OFEV compared with -207 mL/year for placebo*

TOMORROW (Study 1): OFEV demonstrated a 68% relative reduction in the annual rate of FVC decline compared with placebo (-60 mL/year vs -191 mL/year, respectively; *P*=.01, 95% CI=27, 235)[2,8]

CI, confidence interval; HR, hazard ratio.
*The annual rate of decline in FVC (mL/year) was analyzed using a random coefficient regression model.[2]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders

Diarrhea

- Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 11% and discontinuation in 5% of OFEV patients versus 0 and <1% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

Nausea and Vomiting

- Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

proven or probable invasive aspergillosis, specifically, supported the study's primary findings (Lancet 2016 Feb:387:760-9).

Nearly all patients in the study had at least one adverse event, and the proportion with serious adverse events was similar between the treatment groups. However, patients treated with isavuconazole had a significantly lower frequency of hepatobiliary disorders, eye disorders, and skin or subcutaneous disorders.

And overall, significantly fewer patients reported drug-related adverse events with isavuconazole (42% of patients) than with voriconazole (60% of patients). Discontinuation from adverse events, moreover, was significantly less common among isavuconazole-treated patients.

Of the 516 patients in the intention-to-treat group, 53% were confirmed to have proven or probable invasive mold disease, and more than 80% of the mycologically documented cases were *Aspergillus* infections. Enrollment of patients with possible invasive mold disease at the start "reflects the real-life strategy of early initiation of antifungal treatment," the investigators say.

Isavuconazonium sulfate was

Continued on following page

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

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

THE MOST COMMON ADVERSE EVENTS WERE GASTROINTESTINAL IN NATURE AND GENERALLY OF MILD OR MODERATE INTENSITY[2]

- Diarrhea was reported in 62% of patients receiving OFEV vs 18% on placebo
- Diarrhea can be managed by symptomatic treatment, dose reduction, or treatment interruption until diarrhea resolves to levels that allow continuation of therapy. If severe diarrhea persists despite symptomatic treatment, discontinue OFEV

ONE CAPSULE, TWICE DAILY WITH FOOD[2]

Not shown at actual size

Visit hcp.OFEV.com for more information.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

Embryofetal Toxicity: OFEV is Pregnancy category D. It can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential hazard to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV.

Arterial Thromboembolic Events: Arterial thromboembolic events were reported in 2.5% of OFEV and 0.8% of placebo patients, respectively. Myocardial infarction was the most common arterial thromboembolic event, occurring in 1.5% of OFEV and 0.4% of placebo patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. Bleeding events were reported in 10% of OFEV versus 7% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

Gastrointestinal Perforation: OFEV may increase the risk of gastrointestinal perforation. Gastrointestinal perforation was reported in 0.3% of OFEV versus in 0% placebo patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

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

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approved in 2015 by the FDA for the treatment of invasive aspergillosis and invasive mucormycosis. Voriconazole is the current standard for the primary treatment of invasive aspergillosis and is recommended for some other mold infections, but it is not active against mucormycosis and has "highly variable nonlinear pharmacokinetics in adults," which has triggered recommendations for drug monitoring.

Therapeutic monitoring aimed at individualizing dosage regimens to improve response and prevent adverse events became the standard of care in some institutions during the study period (2007-2013). The study used the labeled dose of voriconazole, however, and did not address the efficacy of either drug with drug monitoring.

The study also excluded patients with AIDS, abnormal liver or renal function, and those receiving antifungal prophylaxis with a mold-active triazole – factors that may limit generalizability of the findings.

Funding for the study was provided by Astellas Pharma Global Development and Basilea Pharmaceutica International. Dr. Maertens disclosed receiving nonfinancial support from Astellas and Basilea.

GRANTED BREAKTHROUGH THERAPY DESIGNATION FOR IPF DURING FDA REVIEW[9]

Start your appropriate patients with IPF on OFEV

CONDUCT liver function tests (ALT, AST, and bilirubin) prior to initiating treatment with OFEV (nintedanib)

COMPLETE the OFEV Prescription Form—available at **www.hcp.OFEV.com**—and fax it to one of the participating specialty pharmacies listed on the form

OFFER enrollment in OPEN DOORS™, a patient support program for patients receiving OFEV

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- Adverse reactions reported in ≥5% of OFEV patients included diarrhea, nausea, abdominal pain, liver enzyme elevation, vomiting, decreased appetite, weight decreased, headache, and hypertension.
- The most frequent serious adverse reactions reported in OFEV patients were bronchitis and myocardial infarction. The most common adverse events leading to death in OFEV patients versus placebo were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV versus 1.8% in placebo patients.

DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.
- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Excretion of nintedanib and/or its metabolites into human milk is probable. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

OFHCPISISEP15

Please see brief summary for OFEV on the following pages.

References: 1. Raghu G et al; on behalf of the ATS, ERS, JRS, and ALAT. *Am J Respir Crit Care Med*. 2015;192(2):238-248. **2.** OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2014. **3.** Zappala CJ et al. *Eur Respir J*. 2010;35(4):830-836. **4.** Schmidt SL et al. *Chest*. 2014;145(3):579-585. **5.** du Bois RM et al. *Am J Respir Crit Care Med*. 2011;184(12):1382-1389. **6.** Song JW et al. *Eur Respir J*. 2011;37(2):356-363. **7.** Richeldi L et al; for the INPULSIS Trial Investigators. *N Engl J Med*. 2014;370(22):2071-2082. **8.** Richeldi L et al. *N Engl J Med*. 2011;365(12):1079-1087. **9.** US Food and Drug Administration. http://www.fda.gov/downloads/Regulatory Information/Legislation/FederalFoodDrugandCosmeticActFD-CAct/SignificantAmendmentstothe FDCAct/FDASIA/UCM380724.pdf. Accessed September 1, 2015.

OFEV® (nintedanib) capsules 150mg

Boehringer Ingelheim

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National Sarcoidosis Awareness Month

In conjunction with National Sarcoidosis Awareness Month in April, and in partnership with the Foundation for Sarcoidosis Research (FSR), the CHEST Foundation has launched the second annual *Seek Answers. Inspire Results*. campaign.

Throughout the campaign, the CHEST Foundation and FSR are offering tools for people with sarcoidosis and their caregivers. Among the materials in the provider and patient toolkits is the "Sarcoid Five," a list of five questions designed to start proactive patient-doctor conversations and help people living with sarcoidosis to understand options and create a personalized plan to control their individual condition.

Additional campaign materials include a radio media tour, social media sharable images, infographics, and compelling digital assets, including a video and interactive, Web-based element. Further information can be found at chestnet.org/sarcoid.

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see package insert for full Prescribing Information, including Patient Information

INDICATIONS AND USAGE: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION: Testing Prior to OFEV Administration: Conduct liver function tests prior to initiating treatment with OFEV *[see Warnings and Precautions]*. **Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. **Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions and Adverse Reactions]*. Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times to <5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions and Adverse Reactions]*. Discontinue OFEV for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Elevated Liver Enzymes: The safety and efficacy of OFEV has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Treatment with OFEV is not recommended in patients with moderate or severe hepatic impairment *[see Use in Specific Populations]*. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT). Liver enzyme increases were reversible with dose modification or interruption and not associated with clinical signs or symptoms of liver injury. The majority (94%) of patients with ALT and/or AST elevations had elevations <5 times ULN. Administration of OFEV was also associated with elevations of bilirubin. The majority (95%) of patients with bilirubin elevations had elevations <2 times ULN *[see Use in Specific Populations]*. Conduct liver function tests (ALT, AST, and bilirubin) prior to treatment with OFEV, monthly for 3 months, and every 3 months thereafter, and as clinically indicated. Dosage modifications or interruption may be necessary for liver enzyme elevations. **Gastrointestinal Disorders:** Diarrhea: Diarrhea was the most frequent gastrointestinal event reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to <1% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV (nintedanib). Nausea and Vomiting: Nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, these events were of mild to moderate intensity. Nausea led to discontinuation of OFEV in 2% of patients. Vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **Embryofetal Toxicity:** OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib was teratogenic and embryotoxicidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on an AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use adequate contraception during treatment and at least 3 months after the last dose of OFEV *[see Use in Specific Populations]*. **Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In clinical trials, bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. Use caution when treating patients who have had recent abdominal surgery. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Liver Enzyme and Bilirubin Elevations *[see Warnings and Precautions];* Gastrointestinal Disorders *[see Warnings and Precautions];* Embryofetal Toxicity *[see Warnings and Precautions];* Arterial Thromboembolic Events *[see Warnings and Precautions];* Risk of Bleeding *[see Warnings and Precautions];* Gastrointestinal Perforation *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OFEV was evaluated in over 1000 IPF patients with over 200 patients exposed to OFEV for more than 2 years in clinical trials. OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV (nintedanib), more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse reactions with an incidence of ≥5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

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

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

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

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

DRUG INTERACTIONS: P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exp sure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **Anticoagulants:** Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust

Few pneumonia patients tested for HIV on admission

BY DOUG BRUNK
Frontline Medical News

SAN DIEGO – Only 39% of patients hospitalized for pneumonia underwent HIV testing, even though federal recommendations for universal HIV screening in all health care settings have been in place since 2006, according to the results of a retrospective, single-center study.

"Despite universal recommendations for HIV screening in all health care settings, HIV testing rates remain low among patients hospitalized with pneumonia," Dr. Dana C. Clifton said at an annual scientific meeting on infectious diseases. "A number of patients were subsequently diagnosed with HIV after a prolonged delay."

Of U.S. patients newly diagnosed with HIV, 41% report no prior HIV testing and an estimated 14%-25% of those living with HIV are undiagnosed, said Dr. Clifton, an internist at Duke University Medical Center, Durham, N.C. In 2006, the Centers for Disease Control and Prevention recommended routine HIV screening in all health care settings for all patients aged between 13 and 64 years old.

Dr. Clifton and her associates retrospectively evaluated patients admitted to Duke University Health System during 1996-2014 with a first primary

Routine screening is cost effective, compared with screening tests for colon cancer, diabetes, and breast cancer.

DR. CLIFTON

diagnosis of pneumonia. They used ICD-9 codes for primary diagnosis of pneumonia at time of hospital admission, reviewed a subset of charts to validate the diagnosis, and conducted a random sample of those without prior HIV diagnosis to evaluate HIV testing. The primary outcome was HIV testing during pneumonia admission. Secondary outcomes were documented prior HIV testing in the electronic medical record and subsequent new HIV diagnosis following pneumonia admission.

During the time period studied, 6,858 patients, of which 345 (5%) were previously known to be HIV positive, were admitted with a primary diagnosis of pneumonia. 5,133 of the patients were discharged by general medicine or pulmonary service.

Of the 6,513 not previously known to be HIV positive, 19 (0.3%) were diagnosed with HIV during hospital admission and 46 (0.7%) were diagnosed with HIV a median of 807 days after admission.

IDWeek marks the combined annual meetings of the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The researchers reported having no financial disclosures.

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anticoagulation treatment as necessary *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category D. [See Warnings and Precautions]:* OFEV (nintedanib) can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **Nursing Mothers:** Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV, 60.8% were 65 and over, while 16.3% were 75 and over. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%). No dedicated pharmacokinetic (PK) study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of OFEV (nintedanib) as needed for patients with mild hepatic impairment (Child Pugh A). The safety and efficacy of nintedanib has not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended *[see Warnings and Precautions]*. **Renal Impairment:** Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl) and end-stage renal disease. **Smokers:** Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

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

PATIENT COUNSELING INFORMATION: *Advise the patient to read the FDA-approved patient labeling (Patient Information).* Liver Enzyme and Bilirubin Elevations: Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) *[see Warnings and Precautions]*. Gastrointestinal Disorders: Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV (nintedanib). Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting *[see Warnings and Precautions and Adverse Reactions]*. Pregnancy: Counsel patients on pregnancy planning and prevention. Advise females of childbearing potential of the potential hazard to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of childbearing potential to use adequate contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise female patients to notify their doctor if they become pregnant during therapy with OFEV *[see Warnings and Precautions and Use in Specific Populations]*. Arterial Thromboembolic Events: Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions]*. Risk of Bleeding: Bleeding events have been reported. Advise patients to report unusual bleeding *[see Warnings and Precautions]*. Gastrointestinal Perforation: Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions]*. Nursing Mothers: Advise patients to discontinue nursing while taking OFEV or discontinue OFEV while nursing *[see Use in Specific Populations]*. Smokers: Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using with OFEV. Administration: Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration]*.

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Expiratory central airway collapse in 5% of smokers

BY MARY ANN MOON
Frontline Medical News

Among current and former smokers with or without chronic obstructive pulmonary disease (COPD), expiratory central airway collapse develops in approximately 5% and is associated with a worse respiratory-related quality of life, greater dyspnea, and an increased rate of total and severe exacerbations of pulmonary problems, according to a report published online Feb. 2 in JAMA.

Until recently, expiratory central airway collapse (ECAC) could only be studied using bronchoscopy, so it was not very well characterized. For example, the estimated prevalence among patients with known respiratory problems ranged from 1% to 53%. With the increasing use of noninvasive imaging techniques, the condition is being recognized more often, especially in association with smoking and COPD, but it still remains poorly understood, said Dr. Surya P. Bhatt of the division of pulmonary, allergy, and critical care medicine, University of Alabama at Birmingham, and his associates.

To assess the prevalence and clinical significance of ECAC, the investigators analyzed paired CT images of inspiratory and expiratory scans collected in the multicenter COPDGene study, focusing on scans for 8,820 current and former smokers aged 45-80 years (mean age, 59.7 years) who enrolled from local communities across the United States at 21 participating medical centers. Approximately 57% of the study participants were men, 66% were white and 34% were African American, 52% were active smokers, and 44% had COPD.

A total of 443 cases of ECAC were identified, for a prevalence of 5%.

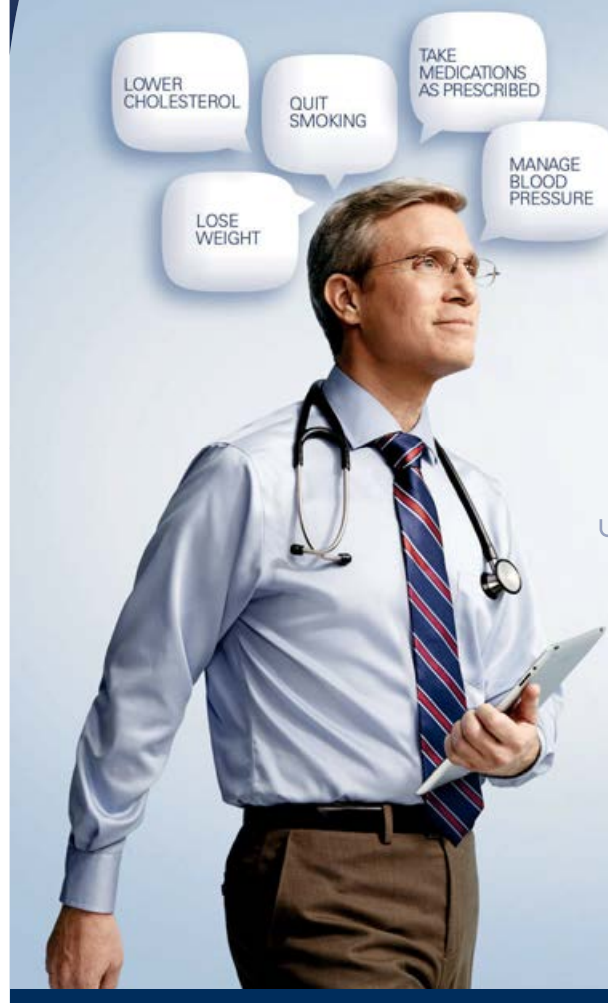
ECAC was more common in participants with COPD (5.9%) than in those without COPD (4.3%), and the prevalence increased with increasing severity of COPD. Study subjects with ECAC were older than those without the condition. ECAC also was more frequent among women than men (7.2% vs 3.1%), and among whites than blacks (6.2% vs 2.5%). Participants with ECAC had a higher body-mass index, a higher prevalence of chronic bronchitis, and more pack-years of smoking than those without ECAC.

In the primary data analysis, adults with ECAC had a worse respiratory-related quality of life than those without the condition, as measured using the St. George's Respiratory Questionnaire. This association remained robust, and was independent of the degree of airflow obstruction and the severity of COPD, after the data were adjusted to account for patient demographics, structural lung disease, and forced expiratory volume in 1 second. "We speculate that ECAC might explain some cases of dyspnea disproportionate to apparent obstructive airways disease measured by CT, spirometry, or both," Dr. Bhatt and his associates said.

Participants with ECAC also had more severe dyspnea as measured by the modified Medical Research

Continued on following page

Of all the things you recommend to protect your patients aged 65+



GET VACCINATED AGAINST PNEUMOCOCCAL PNEUMONIA

HERE'S ONE YOU CAN GET DONE TODAY

Make vaccination a priority.
Help protect your appropriate patients with Prevnar 13®.

- Pneumococcal pneumonia can have serious consequences and may lead to hospitalization[1]
- The CDC's ACIP recommends Prevnar 13® for adults aged 65+[2]
- Prevnar 13® was shown to prevent pneumococcal pneumonia and IPD in a landmark efficacy trial of 84,496 adults aged 65+[3]
- Prevnar 13® is covered by the Medicare Part B FFS benefit for adults aged 65+ with $0 in out-of-pocket costs

Learn more about Prevnar 13® and the information above at www.Prevnar13info.com

ACIP=Advisory Committee on Immunization Practices; CDC=Centers for Disease Control and Prevention; FFS=fee-for-service; IPD=invasive pneumococcal disease.

INDICATION
- In adults 50 years of age and older, Prevnar 13® is indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Limitations of Use and Effectiveness
- Prevnar 13® will only help protect against *S pneumoniae* serotypes in the vaccine

IMPORTANT SAFETY INFORMATION
- Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid–containing vaccine is a contraindication
- Immunocompromised individuals or individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may have reduced antibody response
- In adults, antibody responses to Prevnar 13® were diminished when given with inactivated trivalent influenza vaccine
- In adults, the commonly reported solicited adverse reactions were pain, redness, and swelling at the injection site, limitation of arm movement, fatigue, headache, muscle or joint pain, decreased appetite, chills, or rash

Please see Brief Summary of Prescribing Information on adjacent page(s).

References: 1. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med.* 2013;369(2):155-163. **2.** Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2014;63(37):822-825. **3.** Bonten MJM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med.* 2015;372(12):1114-1125.

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Prevnar 13®
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Continued from previous page

Council score (JAMA 2016 Feb 2. doi: 10.1001/jama.2015.19431).

A subset of 7,456 study participants were assessed at 3- to 6-month intervals for a median of 4.3 years. Compared with participants who did not have ECAC, those who did developed more total exacerbations of pulmonary problems (35 vs. 58 events per 100 person-years) and more severe exacerbations requiring hospitalization (10 vs. 17 events per 100 person-years). Mortality, however, was not significantly different between participants who had ECAC (9.9%) and those who did not (9.6%).

"Whether some of these [exacerbations] represent decompensated ECAC or whether ECAC is a marker for future respiratory events needs to be investigated. Our results suggest that ECAC might contribute to symptoms independent of underlying disease and also may serve as a CT-based biomarker of poor respiratory outcomes," the investigators said.

This study was supported by the National Heart, Lung, and Blood Institute.

Dr. Bhatt reported having no relevant financial disclosures; his associates reported ties to numerous industry sources.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Prevnar 13®
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

This brief summary does not include all of the information needed to use Prevnar 13® safely and effectively. Before prescribing, please consult the full Prescribing Information for Prevnar 13®.

DOSAGE FORMS AND STRENGTHS

Prevnar 13® is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

CONTRAINDICATIONS

Severe allergic reaction (eg, anaphylaxis) to any component of Prevnar 13® or any diphtheria toxoid–containing vaccine.

WARNINGS AND PRECAUTIONS

Management of Allergic Reactions
Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 13®.

Altered Immunocompetence
Data on the safety and effectiveness of Prevnar 13® when administered to immunocompromised individuals including those at higher risk for invasive pneumococcal disease (eg, individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome) are not available. Individuals in these groups may have reduced antibody response to active immunization due to impaired immune responsiveness.

Apnea in Premature Infants
Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13®, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. As with any vaccine, there is the possibility that broad use of Prevnar 13® could reveal adverse reactions not observed in clinical trials.

Clinical Trials Experience With Prevnar 13® in Infants and Toddlers
The safety of Prevnar 13® was evaluated in 13 clinical trials in which 4729 infants and toddlers received at least 1 dose of Prevnar 13® and 2760 infants and toddlers received at least 1 dose of Prevnar® active control. Overall, the safety data show a similar proportion of Prevnar 13® and Prevnar® subjects reporting serious adverse events. Among US study subjects, a similar proportion of Prevnar 13® and Prevnar® recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

Serious Adverse Events in All Infant and Toddler Clinical Studies
Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13® recipients and 7.2% among Prevnar® recipients. Serious adverse events observed during different study periods for Prevnar 13® and Prevnar®, respectively, were: 1) 3.7% and 3.5% from dose 1 to the bleed approximately 1 month after the infant series; 2) 3.6% and 2.7% from the bleed after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the bleed approximately 1 month after the toddler dose; and 4) 2.5% and 2.8% during the 6-month follow-up period after the last dose.

The most commonly reported serious adverse events were in the "Infections and infestations" system organ class, including bronchiolitis (0.9%, 1.1%), gastroenteritis (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Prevnar 13® and Prevnar®, respectively.

There were 3 (0.063%) deaths among Prevnar 13® recipients and 1 (0.036%) death among Prevnar® recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age-specific background rates of SIDS from the year 2000.

Among 6839 subjects who received at least 1 dose of Prevnar 13® in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4204 subjects who received at least 1 dose of Prevnar® in clinical trials conducted globally, there were 3 hypotonic-hyporesponsive episode adverse reactions reported (0.071%). All 4 events occurred in a single clinical trial in Brazil in which subjects received whole cell pertussis vaccine at the same time as Prevnar 13® or Prevnar®.

Solicited Adverse Reactions in the 3 US Infant and Toddler Studies
A total of 1907 subjects received at least 1 dose of Prevnar 13® and 701 subjects received at least 1 dose of Prevnar® in the 3 US studies.

Solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13® or Prevnar® administered to US infants and toddlers were: in infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%).

Unsolicited Adverse Reactions in the 3 US Infant and Toddler Safety Studies
The following were determined to be adverse drug reactions based on experience with Prevnar 13® in clinical trials: reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash; and reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

Clinical Trials Experience With Prevnar 13® in Adults Aged ≥50 Years
The safety of Prevnar 13® was assessed in 7 clinical studies (Studies 6-12) conducted in the US and Europe, which included 90,694 adults (47,907 received Prevnar 13®) ranging in age from 50 through 101 years.

The 47,907 Prevnar 13® recipients included 2616 adults who were aged 50 through 64 years and 45,291 adults aged 65 years and older. Of the 47,907 Prevnar 13® recipients, 45,991 adults had not previously received PPSV23 ("PPSV23 unvaccinated") and 1916 adults were previously vaccinated ("PPSV23 previously vaccinated") with PPSV23 at least 3 years prior to enrollment.

Serious Adverse Events in Adult Clinical Studies
Across the 6 safety and immunogenicity studies, serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5055 subjects vaccinated with Prevnar 13® and in 0.4%-1.7% of 1124 subjects vaccinated after an initial study dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23). From 1 month to 6 months after an initial study dose, serious adverse events were reported in 1.2%-5.8% of subjects vaccinated during the studies with Prevnar 13® and in 2.4%-5.5% of subjects vaccinated with PPSV23. One case of erythema multiforme occurred 34 days after receipt of a second dose of Prevnar 13®.

Twelve of 5667 (0.21%) Prevnar 13® recipients and 4 of 1391 (0.29%) PPSV23 recipients died. Deaths occurred between day 3 and day 309 after study vaccination with Prevnar 13® or PPSV23. Two of 12 deaths occurred within 30 days of vaccination with Prevnar 13® and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving Prevnar 13® administered with trivalent inactivated influenza vaccine (TIV) and the other death was due to peritonitis 20 days after receiving Prevnar 13®. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Prevnar 13® were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1), and septic shock (1).

In an efficacy study of subjects 65 years of age and older, serious adverse events within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Prevnar 13® recipients (352 events) and in 314 of 42,225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1006 (7%) Prevnar 13® vaccinated subjects (90 events) and 60 of 1005 (6%) placebo vaccinated subjects (69 events) reported serious adverse events.

During the follow-up period (average of 4 years) for case accumulation there were 3006 deaths (7.1%) in the Prevnar 13® group and 3005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevnar 13® group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Prevnar 13® group and 144 deaths (0.3%) in the placebo group within 29 days – 6 months following vaccination. These data do not provide evidence for a causal relationship between deaths and vaccination with Prevnar 13®.

Solicited Adverse Reactions in Adult Clinical Studies
In adults aged 50 years and older, the commonly reported solicited adverse reactions were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), chills (>5%), or rash (>5%).

Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Prevnar 13® and TIV (Fluarix)
The safety of concomitant administration of Prevnar 13® with TIV was assessed in 2 studies in PPSV23 unvaccinated adults aged 50 through 59 years and aged ≥65 years.

Frequencies of local reactions within 14 days post-vaccination in adults aged 50 through 59 years and in adults aged ≥65 years were similar after Prevnar 13® was administered with TIV compared to Prevnar 13® administered alone, with the exception of mild redness at the injection site, which was increased when Prevnar 13® was administered concomitantly with TIV.

An increase in some solicited systemic reactions within 14 days post-vaccination was noted when Prevnar 13® was administered concomitantly with TIV compared with TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with Prevnar 13® given alone (fatigue, headache, chills, decreased appetite, and joint pain).

Clinical Trials Experience With Prevnar® in Infants and Toddlers
The safety experience with Prevnar® is relevant to Prevnar 13® because the 2 vaccines share common components.

Generally, the adverse reactions reported in clinical trials with Prevnar 13® were also reported in clinical trials with Prevnar®.

Overall, the safety of Prevnar® was evaluated in a total of 5 clinical studies in the United States in which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age.

Adverse events reported in clinical trials with Prevnar® that occurred within 3 days of vaccination in infants and toddlers and resulted in emergency room visits or hospitalizations, but were not presented in Section 6.1 as adverse reactions for Prevnar 13®, are listed below:

Bronchiolitis, UTI, acute gastroenteritis, asthma, aspiration, breath holding, influenza, inguinal hernia repair, viral syndrome, URI, croup, thrush, wheezing, choking, conjunctivitis, pharyngitis, colic, colitis, congestive heart failure, roseola, and sepsis.

Post-marketing Experience With Prevnar® in Infants and Toddlers
The following adverse events have been reported through passive surveillance since market introduction of Prevnar® and, therefore, are considered adverse events for Prevnar 13® as well. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Administration site conditions: Injection site dermatitis, injection site pruritus, injection site urticaria

Blood and lymphatic system disorders: Lymphadenopathy localized to the region of the injection site

Immune system disorders: Anaphylactic/anaphylactoid reaction including shock

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apnea

DRUG INTERACTIONS

Concomitant Immunizations
In clinical trials with infants and toddlers, Prevnar 13® was administered concomitantly with the following US licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [*Haemophilus* b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first 3 doses and with PedvaxHIB [*Haemophilus* b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella, and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A Vaccine, Inactivated] (HepA) for dose 4.

In adults, Prevnar 13® was administered concomitantly with US licensed Fluarix (TIV) for the 2007/2008 influenza season. There are no data on the concomitant administration of Prevnar 13® with diphtheria toxoid–containing vaccines and other vaccines licensed for use in adults 50 years of age and older.
When Prevnar 13® is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevnar 13® with other vaccines/products in the same syringe.

Immunosuppressive Therapies
Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

Antipyretics
A post-marketing clinical study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13®. The data show that 3 doses of acetaminophen (the first dose administered at the time of each vaccination and the subsequent doses at 6 to 8 hour intervals) reduced the antibody response to some serotypes following the third dose of Prevnar 13®, compared with responses among infants who received antipyretics only as needed for treatment. Reduced antibody responses were not observed after the fourth dose of Prevnar 13® when acetaminophen was administered prophylactically.

Prior Vaccination With PPSV23
Prior receipt of Pneumovax® 23 (23 valent pneumococcal vaccine polyvalent, PPSV23) within 1 year results in diminished immune responses to Prevnar 13® compared to PPSV23 naïve individuals.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B
A developmental and reproductive toxicity study has been performed in female rabbits at a dose approximately 20 times the human dose (on mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to Prevnar 13®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether this vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prevnar 13® is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of Prevnar 13® in children below the age of 6 weeks or on or after the 6th birthday have not been established.

Immune responses elicited by Prevnar 13® among infants born prematurely have not been specifically studied.

Geriatric Use
Of the total number of Prevnar 13® recipients aged 50 years and older in clinical studies (N=47,907), 94.5% (45,291 of 47,907) were 65 years and older and 30.3% (14,498 of 47,907) were 75 years and older.

High Risk Populations
Individuals with the diseases or conditions listed below are at increased risk of pneumococcal disease. Immunogenicity and safety data in these populations are limited.

Infants Born Prematurely
Immune responses elicited by Prevnar 13® administered on a US schedule to preterm infants have not been studied. When preterm infants (<37 weeks gestational age, N=100) were administered 4 doses of Prevnar 13® on a non-US schedule, the serotype-specific IgG antibody responses after the third and fourth dose were lower compared to responses among term infants (≥37 weeks gestational age, N=100) for some serotypes; the effectiveness of Prevnar 13® in preterm infants cannot be established from this study.

Children With Sickle Cell Disease
In an open-label, single-arm, descriptive study, 2 doses of Prevnar 13® were administered 6 months apart to children ≥6 to <18 years of age with sickle cell disease who previously received PPSV23 at least 6 months prior to enrollment. Children with a prior history of pneumococcal conjugate vaccination were excluded. For all vaccine serotypes, anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after the first dose compared to pre-vaccination (N=95-131); OPA GMTs following the first and second dose were comparable. The effectiveness of Prevnar 13® in this specific population has not been established.

Adults With HIV Infection
In an open-label, single-arm, descriptive study, 3 doses of Prevnar 13® were administered 6 months apart to HIV-infected adults ≥50 years of age (median age 55 years), with CD4 counts ≥200 cells/μL and serum HIV RNA titer <50,000 copies/mL. All subjects had been vaccinated previously with PPSV23 at least 6 months prior to enrollment. For all vaccine serotypes anti-pneumococcal OPA GMTs were higher after the first dose compared to pre-vaccination (N=94-108); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Prevnar 13® in this specific population has not been established.

PATIENT COUNSELING INFORMATION

Potential Benefits and Risks
Prior to administration of this vaccine, the health care professional should inform the individual, parent, guardian, or other responsible adult of the following potential benefits and risks of immunization with Prevnar 13® *[see Warnings and Precautions (5) and Adverse Reactions (6)]*, the importance of completing the immunization series for their child(ren) unless contraindicated, and that any suspected adverse reactions should be reported to their healthcare professional.

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Interstitial lung abnormalities linked to high death risk

BY MARY ANN MOON
Frontline Medical News

In four large, separate research cohorts in which middle-aged and older participants underwent lung CT, interstitial lung abnormalities were associated with a higher-than-average risk of death within 3-9 years, according to a report published online in JAMA.

These imaging abnormalities were defined as specific patterns of increased lung density affecting more than 5% of any lung zone and included reticular or ground-glass abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, traction bronchiectasis, or pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease. They were identified in approximately 7% of the 11,691 study participants. The study findings, taken together with those of previous research, "demonstrate that despite often being undiagnosed and asymptomatic, interstitial lung abnormalities may be associated with lower survival rates among older persons," said Dr. Rachel K. Putman of the pulmonary and critical care division at Brigham and Women's Hospital and Harvard Medical School, Boston, and her associates.

Previously, interstitial lung abnormalities have been found in the same proportion, 7%, of the general population and have been associated with reduced lung capacity, exercise capacity, and gas exchange. The investigators hypothesized that "the presence of interstitial lung abnormalities would be associated with an increased rate of mortality."

To test this hypothesis, they analyzed data from four large study cohorts that included lung CT: 2,633 participants in the Framingham Heart Study (median follow-up of 4 years after CT), 5,320 in the Age Gene/Environment Susceptibility (AGES)-Reykjavik study (median follow-up, 8.9 years), 2,068 in the Genetic Epidemiology of COPD (COPDGene) study (median follow-up, 6.5 years), and 1,670 participants in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (median follow-up, 2.9 years).

The absolute rates of all-cause mortality were significantly higher among participants who had interstitial lung abnormalities than among those who did not. Mortality rates were 7% vs. 1% in the FHS, 56% vs. 33% in AGES-Reykjavik, 16% vs. 11% in COPDGene, and 11% vs. 5% in ECLIPSE. After the data were adjusted to account for confounding factors such as age, sex, race, body-mass index, current smoking status, and pack-years of smoking, the lung abnormalities remained strongly associated with a higher risk of death in the FHS (hazard ratio, 2.7), AGES-Reykjavik (HR, 1.3), COPDGene (HR, 1.8), and ECLIPSE (HR, 1.4) studies.

The association remained robust in further analyses restricted only to nonsmoking participants, Dr. Putman and her associates said (JAMA. 2016 Feb 16;315[7]672-81. doi: 10.1001/jama.2016.0518).

The AGES-Reykjavik study was the only one to assess causes of death. In that cohort, participants who had interstitial lung abnormalities were more likely to die of a respiratory cause (13%) than were those who had no such abnormalities (4%) or those who had indeterminate findings on lung CT (6%). After the data were adjusted to account for confounding factors, participants with interstitial lung abnormalities were at much higher risk of dying from a respiratory cause (OR, 2.4) such as respiratory failure or pulmonary fibrosis.

This study was supported by the National Institutes of Health; the Icelandic Research Fund; the Lanspitali Scientific Fund; the National Cancer Institute; the National Heart, Lung, and Blood Institute; GlaxoSmithKline; the National Institute on Aging; the Icelandic Heart Association; and the Icelandic Parliament. Dr. Putman reported having no relevant financial disclosures; her associates reported numerous ties to industry sources.

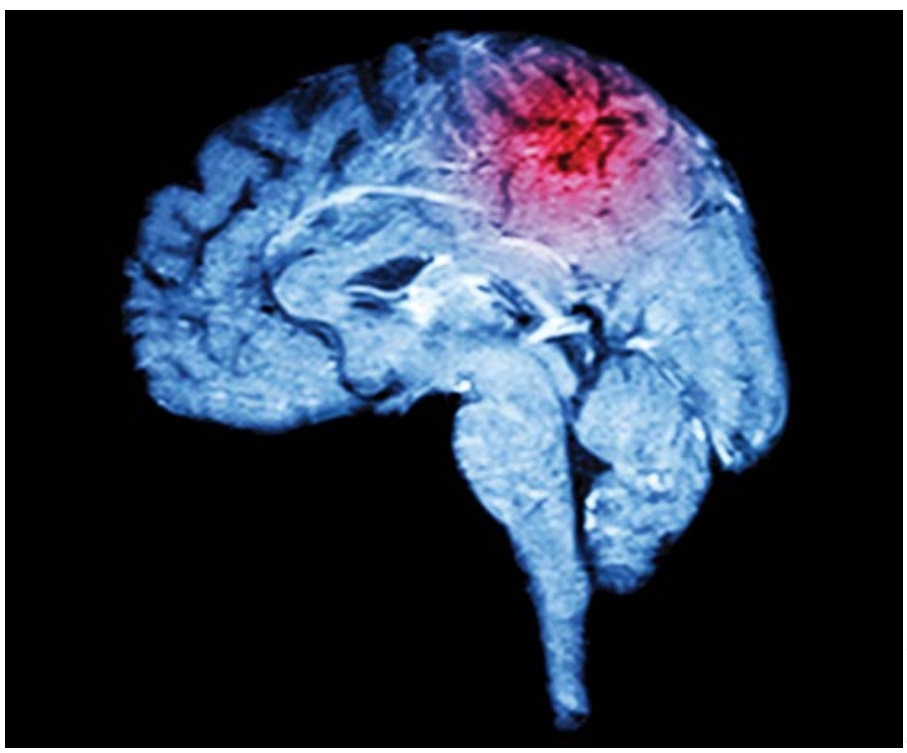
COPD exacerbation amps up stroke risk

BY NICOLA GARRETT
Frontline Medical News

People with chronic obstructive pulmonary disease have an approximately 20% increased risk of stroke, and the risk is highest during the time after an acute exacerbation of COPD, data from a large epidemiologic study indicate.

The study also indicated that cigarette smoking was a strong risk factor for stroke and that hypertension management is important in COPD patients given the elevated risk for hemorrhagic strokes observed, according to Dr. Marileen L. P. Portegies of Erasmus MC University Medical Center, Rotterdam, the Netherlands, and her colleagues.

In 13,115 participants from the Rotterdam study, people with COPD had a 6.7-fold increase in the risk of stroke within the first 7 weeks of a severe exacerbation (hazard ratio, 6.66; 95% confidence interval, 2.42-18.20).



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The study (Am J Respir Crit Care Med. 2016; 193:251-8) found that 1,250 of the participants had a stroke (701 were ischemic and 107 hemorrhagic) over 126,347 person-years of follow-up.

After researchers adjusted for age and sex, COPD was significantly associated with all stroke (HR, 1.20), ischemic stroke (HR, 1.27), and hemorrhagic stroke (HR, 1.70).

Smoking was the strongest explanatory factor for the association between COPD and stroke, the researchers said. Adjustments for cardiovascular risk factors gave similar effect sizes, whereas adjustments for smoking attenuated the effect sizes: for all stroke, (HR, 1.09); for ischemic stroke, (HR, 1.13) ; and for hemorrhagic stroke, (HR 1.53) .

"Our study reveals the importance of smoking as a shared risk factor and implicates that clinicians should be aware of the higher risk of both stroke subtypes in subjects with COPD, especially after severe exacerbations," they concluded. Smoking failed to account for the period of a COPD exacerbation during which risk for strokes and MIs increase.

VIEW ON THE NEWS

Dr. Daniel R. Ouellette, FCCP, comments: Originally thought to be a disease of just the lungs, COPD is now recognized as a condition associated with effects on multiple organ systems. Practitioners are learning that COPD patients have an increased incidence of other conditions such as cardiovascular disease, the metabolic syndrome, various neoplasms, osteoporosis, and cognitive disorders, to name a few. Stroke can now be added to this list. A large study from the Netherlands indicates that stroke is closely associated with acute exacerbations of COPD. Intriguingly, the shared association of smoking between COPD and stroke did not account for all of the risk of association, suggesting that the underlying pathophysiology of a COPD exacerbation may play a role.

Survey finds inconsistencies in delirium screening

BY KARI OAKES
Frontline Medical News

ORLANDO – Most of the ICU directors responding to a survey had delirium screening protocols in place, but said their current practices don't conform to best practice guidelines.

"While most ICUs have protocols that incorporate delirium screening with a validated tool, most perceived current delirium prevention and treatment strategies do not reflect best evidence or current pain, agitation, and delirium practice guidelines," senior author Amy Dzierba, Pharm.D., said in an interview. Practice guidelines for pain, agitation, and delirium in the ICU, promulgated jointly by the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM) in 2013, call for ICU patients to be screened regularly for delirium, and recommend non-pharmacologic and pharmacologic interventions to prevent, or reduce the duration of, delirium in critically ill adults.

The Critical Care Pharmacy Trials Network (CCPTN) initiated the survey. Responses came from 19 hospitals with 42 ICUs, with 74% of them being academic medical centers and the remainder teaching community hospitals. Joshua Swan, Pharm.D. of Texas Southern University, Houston, presented the study findings at the Society for Critical Care Medicine's annual Critical Care Congress.

The multicenter, observational, cross-sectional study used a validated, web-based survey that included questions about demographic characteristics of the ICUs, as well as a series of 36 questions about perceptions of delirium screening, prevention, and treatment practices.

Most ICUs (26/42, 62%) used the Confusion Assessment Method for the ICU (CAM-ICU), while another 10 hospitals (24%) used the Intensive Care Delirium Screening Checklist Worksheet (ICDSC). The other hospitals used physician or nurse opinion, or another method.

Twenty-two of 42 respondents (58%) judged that they screened for delirium twice daily; 10 ICUs thought they screened three times daily, three screened once daily, and the rest thought they screened more frequently than twice daily.

A non-pharmacologic delirium prevention and reduction protocol was in place for 33 (80%) of the ICUs. Specific interventions that respondents judged they used, regardless of delirium presence, included reorientation in more than 80% of ICUs, catheter and restraint removal in more than 70% of ICUs responding, and ensuring eyeglasses were donned for about 70% of ICUs.

Less frequently-used interventions were provision of hearing aids, early mobilization, reduction of unnecessary noise and stimulation, music therapy, provision of earplugs, and cognitive exercises.

About half of survey respondents said that their ICUs used early mobilization as a delirium prevention strategy.

Perceived pharmacologic strategies that were used in about half of the ICUs for patients without delirium included avoidance of benzodiazepines for sedation, minimization of anticholinergic medication, and minimization of caffeine.

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"Future studies should compare actual practices to those that are perceived," said Dr. Dzierba, clinical pharmacy manager for adult critical care at Columbia University Medical Center's New York-Presbyterian Hospital. Dr. Dzierba reported no external source of funding for the study, and the authors had no relevant conflicts of interest to disclose.

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Tool forecasts performance at 1 year after ICU stay

BY KARI OAKES
Frontline Medical News

ORLANDO – A new clinical prediction rule correlates well with performance status at 1 year after ICU hospitalization in patients over age 80.

Illness severity, comorbidities, baseline frailty, a primary diagnosis of stroke, and being male were all predictors of poor performance status at 1 year. A primary diagnosis of emergency coronary artery bypass grafting or valve replacement, a high baseline performance status, and being married were associated with good performance status at 1 year. The c-statistic for the model, a standard indicator of predictive power, was 0.811, a figure that indicates good predictive ability.

The findings from the REALISTIC 80 (Realities, Expectations,and Attitudes to Life Support Technologies in Intensive Care for Octogenarians) study of 17 patient and illness characteristics allowed Dr. Daren Heyland, professor of medicine and epidemiology at Queen's University, Kingston, Ont., and his coinvestigators in the Canadian Critical Care Trials Group (CCCTG), to conclude that eight factors were most predictive of performance status at 12 months for ICU patients aged 80 and over. REALISTIC 80 is a CCCTG project

The values for the predictors are derived from responses to an online guided questionnaire called the ICU Workbook. The questionnaire is completed by patients' family members or surrogates, and the responses are used to calculate the values that constitute the clinical prediction rule's components.

Gathering this information may help health care providers and family members in end-of-life decision making, said Dr. Heyland, who is also director of CARENET, which hosts the online guided questionnaire and is an affiliation of Canadian researchers focused on end-of-life care. He spoke at the Society of Critical Care Medicine's Critical Care Congress.

"For the very elderly, it is plausible that poor communication and decision making lead to overutilization of ICU resources and poor-quality end-of-life care," he said.

REALISTIC 80 enrolled 434 patients, aged 80-100 years (mean age, 84.6) who were admitted to ICUs at participating institutions. The primary outcome measure of REALISTIC 80 was the 12-month survival and health-related quality of life; "recovery from critical illness" was defined as a Palliative Performance Scale (PPS) score of greater than or equal to 60% at 12 months.

'For the very elderly, it is plausible that poor communication and decision making lead to overutilization of ICU resources and poor-quality end-of-life care.'

Patients scoring at 60% on the 0%-100% scale of this functional status measure may have reduced ambulation, be unable to engage in housework or hobbies, have significant disease, need assistance, and be confused at times. An advantage of this scale, said Dr. Heyland, is that it eliminates survivorship bias in analyzing data, since a score of 0 is assigned to individuals who die. About 50% of patients had died by 12 months; about 21% were alive, with a reduced health status below the threshold of 60 on the PPS; and about 29% were alive, with a PPS score above the predetermined quality of life threshold. About 17% of participants were lost to follow-up. The predictive model was derived from completed cases, and a sensitivity analysis using imputed data for missing patients showed that it retained its predictive value.

Dr. Heyland said the presence of advance directives didn't appear to affect outcomes.

Dying in the ICU after days of mechanical ventilation or surviving with very low performance status "doesn't sound like good quality of life to me, and it illustrates the challenge we have as clinicians in getting to what's best for patients," he said.

The study was funded by the Canadian Institutes of Health Research and conducted under the auspices of the CCCTG and CARENET. The study investigators reported no other relevant financial disclosures.

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Ebola patients treated in the West showed 81.5% survival

BY MARY ANN MOON
Frontline Medical News

Overall survival was 81.5% for the 27 patients with Ebola virus infection who were treated in the United States or Europe during the recent outbreak, according to a report published online Feb. 18 in the New England Journal of Medicine.

This is markedly higher than the 37%-74% survival reported for the almost 29,000 cases treated in West Africa, where treatment centers were challenged by overwhelming numbers of critically ill patients; limited medical supplies; insufficient numbers of caregivers; limited water, electricity, refrigeration, and other basic resources; and hot, humid working conditions that reduced the time health care personnel could attend to patients while wearing the required protective gear, said Dr. Timothy M. Uyeki of the Centers for Disease Control and Prevention, Atlanta, and his associates.

The investigators performed a retrospective analysis of the medical records of these 27 patients in a descriptive study of their clinical care. The patients were treated from August 2014 through December 2015 at 15 hospitals in 9 countries. Twenty (74%) were medically evacuated from West Africa, three (11%) were Western health care personnel who acquired the disease while caring for patients, and four were "imported" patients who contracted the virus while in West Africa but didn't become ill until after they traveled to the United States or Europe. Overall, 22 of the patients (81%) were health care personnel, of whom 17 (77%) contracted the virus in West Africa.

Overall mortality was 11.1% after 2 weeks of illness and 18.5% after 4 weeks. The five patients who died were all aged 42 years or older and were significantly older than those who survived. Being 40-45 years old or older has been identified as a risk factor in West Africa as well.

Those who died also were hospitalized significantly later after the onset of illness. At least six more patients would have died if they hadn't received advanced organ support: two required noninvasive ventilation, two required invasive mechanical ventilation, and two required both invasive mechanical ventilation and continuous renal-replacement therapy.

Routine therapies included oral or intravenous fluid replacement, total parenteral nutrition, antiemetics, empiric treatment with multiple antibiotics, nonconvalescent blood products, and respiratory supportive care. Most patients also received investigative therapies such as monoclonal antibody cocktails, antivirals, and treatments aimed at counteracting vascular leakage.

A wide range of possible adverse effects were reported – including systemic inflammatory response syndrome, hypotension, elevated aminotransferase levels, and transfusion-associated acute lung injury – but couldn't be distinguished from the effects of supportive treatments or even of the virus itself "because of their uncontrolled administration and because most patients received multiple, overlapping investigational therapies," the researchers said (N Engl J Med. 2016 Feb 18;374:636-46. doi: 10.1056/NEJMoa1504874).

"A key feature" of the lifesaving clinical care was laboratory testing to closely monitor electrolyte levels and hematologic factors.

"Our experience suggests that early presentation and receipt of supportive care, IV fluid resuscitation, careful fluid management and electrolyte replacement to correct metabolic abnormalities, nutritional support, and critical care support may reduce mortality among patients with Ebola virus disease," Dr. Uyeki and his associates said.

Eight (30%) of the patients in this study presented with cough and nine required ventilatory assistance, and difficulty breathing raised the risk of death.

They noted that, until now, the Ebola virus infection was not thought to involve a clinically significant respiratory component, and that the "pathophysiological mechanism of pulmonary disease in patients with Ebola virus infection is unknown."

This study was supported by the working group of the U.S.–European Clinical Network on Clinical Management of Ebola Virus Disease Patients in the U.S. and Europe. Dr. Uyeki reported having no relevant financial disclosures; two of his associates reported ties to Epiguard and Pfizer.

Periop statins don't avert acute kidney injury

BY KARI OAKES
Frontline Medical News

ORLANDO – Statins administered perioperatively offered no protection against acute kidney injury following cardiac surgery, according to new results of a 5-year randomized clinical trial.

The findings held true whether or not patients were naive to statins; serum creatinine levels actually increased significantly more for statin-naive patients given atorvastatin than those given placebo.

Dr. Billings: Continuing or withdrawing statin treatment doesn't affect AKI.

The study was stopped early for patients naive to statins because increased acute kidney injury was seen in those patients who had chronic kidney disease (eGFR less than 60 mL/min/1.73 m^2), and was subsequently stopped early for futility for all patients.

"De novo initiation of daily perioperative atorvastatin treatment did not reduce the incidence of AKI or reduce the increase in serum creatinine concentration associated with cardiac surgery," wrote Dr. Frederic T. Billings IV, professor of medicine at Vanderbilt University, Nashville, Tenn., and his collaborators. The findings (JAMA 2016 Feb 23. doi: 10.1001/jama.2016.0548) were published concurrently with his presentation at the Critical Care Congress, sponsored by the Society of Critical Care Medicine.

In what Dr. Phil B. Fontanarosa, executive editor of JAMA and co-moderator of the late-breaking trials session at the meeting, described as "really an elegant clinical trial," Dr. Billings and his collaborators enrolled 615 patients over 5 years at Vanderbilt University Medical Center.

Patients undergoing elective coronary artery bypass grafting, valvular heart surgery, or ascending aortic surgery were eligible. Patients were excluded if they had prior statin intolerance, acute coronary syndrome, or liver dysfunction; were taking potent CYP3A4 inhibitors or cyclosporine; were receiving renal replacement therapy or had a kidney transplant; or were pregnant.

Both patients currently on a statin and patients naive to statins were recruited. Statin-naive patients received 80 mg atorvastatin the day before surgery, and then 40 mg of atorvastatin on the day of surgery and daily following surgery, or a matched placebo regimen.

Patients who were already on a statin received the study drug only on days that they would not have

Indication

IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

There's marking time...

and there's making memories

Efficacy was demonstrated in the IFUM* study

- IRESSA achieved a 50% objective response rate (ORR) (95% confidence interval [CI]: 41, 59) by blinded independent central review (BICR) and a 70% ORR (95% CI: 61, 78) by investigator assessment

Efficacy was confirmed by the IPASS† study

- 3.5-month improvement in progression-free survival (median) vs chemotherapy—10.9 months with IRESSA vs 7.4 months with carboplatin/paclitaxel (HR=0.54; 95% CI: 0.38, 0.79) by BICR

Safety was established in the ISEL‡ study

- The most frequent adverse reactions were (incidence of >20% and greater than placebo) reported in IRESSA-treated patients were skin reactions (47%) and diarrhea (29%)
- ≤5.1% of IRESSA-treated patients experienced severe adverse reactions
- Approximately 5% of IRESSA-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event; the most frequent adverse reactions that led to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%)

received a statin if treated according to the current standard of care. It was deemed unethical to allow those patients to receive placebo during and after surgery, since observational studies suggested that doing so might increase their potential for AKI.

For those patients already on a statin, this meant that they stayed on their usual regimen until the day of surgery, and then were randomized to receive either 80 mg of atorvastatin on the day of surgery and 40 mg of atorvastatin the day after surgery, or a matching placebo regimen.

For both groups, the study drug was given at least 3 hours before surgery on the day of surgery.

Randomization was stratified for prior statin use, for chronic kidney disease, and by history of diabetes. The 199 patients naive to statins and the 416 already on a statin were similar in demographic and health characteristics. Median age was 67 years, 188 (30.6%) were women; 202 participants (32.8%) had diabetes.

The primary outcome measure was diagnosis of AKI, defined as an increase of 0.3 mg/dL in serum creatinine, or beginning renal replacement therapy within 48 hours of surgery. Baseline serum creatinine was measured no more than 7 days prior to surgery.

Continued on following page

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

Important Safety Information

- There are no contraindications for IRESSA
- Interstitial Lung Disease (ILD) or ILD-like reactions (eg, lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of 2462 IRESSA patients; of these, 0.7% were Grade ≥3 and 3 cases were fatal. Withhold IRESSA and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. Permanently discontinue IRESSA if ILD is confirmed
- In patients who received IRESSA, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Grade ≥3 liver test abnormalities occurred in 5.1% ALT, 3.0% AST, and 0.7% bilirubin of patients. The incidence of fatal hepatotoxicity was 0.04%. Obtain periodic liver function testing. Withhold IRESSA in patients with worsening liver function and discontinue in patients with severe hepatic impairment
- Gastrointestinal perforation occurred in three (0.1%) of 2462 IRESSA patients. Permanently discontinue IRESSA in patients who develop gastrointestinal perforation
- Grade ≥3 diarrhea occurred in 3% of 2462 IRESSA patients. Withhold IRESSA for severe or persistent (up to 14 days) diarrhea
- Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blepharitis and dry eye (6.7%)] occurred in 2462 IRESSA patients. The incidence of Grade 3 ocular disorders was 0.1%. Interrupt or discontinue IRESSA for severe or worsening ocular disorders
- Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been reported from treatment with IRESSA. Erythema multiforme and dermatitis bullous have been reported in two patients (0.08%) across NSCLC trials. IRESSA treatment should be interrupted or discontinued if patients develop severe bullous, blistering or exfoliating conditions
- Based on its mechanism of action and data from animal reproduction studies IRESSA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy
- Advise women to discontinue breast-feeding during treatment with IRESSA
- The most commonly reported adverse drug reactions reported in more than 20% of patients and greater than placebo, were skin reactions (47%) and diarrhea (29%)

Please see brief summary of complete Prescribing Information on adjacent pages.

*IRESSA efficacy was evaluated in a multicenter, single-arm, open-label study as a first-line treatment of 106 Caucasian patients with EGFR mutation–positive metastatic NSCLC. IFUM=IRESSA Follow-Up Measure.

†IPASS included an exploratory analysis of a subset of a randomized, multicenter, open-label trial conducted in patients with metastatic adenocarcinoma histology NSCLC receiving first-line treatment. Patients received IRESSA 250 mg orally once daily (n=88) or up to 6 cycles of carboplatin/paclitaxel (n=98). IPASS=IRESSA Pan-Asia Study.

†Common adverse reactions were evaluated in ISEL, a randomized, multicenter, double-blind, placebo-controlled study of 1692 metastatic NSCLC patients. Patients received IRESSA 250 mg daily (n=1126) or placebo (n=562). ISEL=IRESSA Survival Evaluation in Lung Cancer. A pooled safety database from 3 randomized trials was used to evaluate for serious and uncommon adverse drug reactions.

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Continued from previous page

AKI occurred in 64 of 308 patients (20.8%) in the atorvastatin group, and in 60 of 307 patients (19.5%) receiving placebo overall ($P = .75$). For those naive to statins, 21.6% of the atorvastatin group and 13.4% of the placebo group developed AKI ($P = .15$). Overall, 179 enrolled patients had CKD, and the incidence of AKI did not significantly differ in the atorvastatin and the placebo arms of this subgroup.

The subpopulation of participants with CKD who were statin naive (n = 36), however, saw an increased incidence of AKI with atorvastatin compared to placebo. AKI occurred in 9 of 17 patients (52.9%) given atorvastatin, and in 3 of 19 (15.8%) given placebo group (RR, 3.35[95% confidence interval 0.12 to 10.05]; $P = .03$). "It should be noted that the number of patients in this subgroup was particularly small, leading to a wide confidence interval and an increased chance of type 1 error," said Dr. Billings.

Secondary outcome measures were maximum increase in creatinine concentration from baseline through postop day 2, delirium in the ICU, degree of myocardial injury, and incidence of postoperative pneumonia, atrial fibrillation, or stroke. Perioper-

IRESSA® (gefitinib) tablets for oral use

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert

INDICATIONS AND USAGE
IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test *[see Clinical Studies (14) in the full Prescribing Information]*.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations *[see Clinical Studies (14) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection
Select patients for the first-line treatment of metastatic NSCLC with IRESSA based on the presence of EGFR exon 19 deletion or exon 21 (L858R) substitution mutations in their tumor *[see Indications and Usage (1)* and *Clinical Studies (14) in the full Prescribing Information]*. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dose
The recommended dose of IRESSA is 250 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Do not take a missed dose within 12 hours of the next dose.

Administration to Patients Who Have Difficulty Swallowing Solids
Immerse IRESSA tablets in 4 to 8 ounces of water by dropping the tablet in water, and stir for approximately 15 minutes. Immediately drink the liquid or administer through a naso-gastric tube. Rinse the container with 4 to 8 ounces of water and immediately drink or administer through the naso-gastric tube.

Dose Modification
Dose Modifications for Adverse Drug Reactions

Withhold IRESSA (for up to 14 days) for any of the following:
- Acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever) *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- NCI CTCAE Grade 2 or higher in ALT and/or AST elevations [*see Warnings and Precautions (5.2) in the full Prescribing Information*]
- NCI CTCAE Grade 3 or higher diarrhea *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Signs and symptoms of severe or worsening ocular disorders including keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- NCI CTCAE Grade 3 or higher skin reactions *[see Warnings and Precautions (5.6) in the full Prescribing Information]*

Resume treatment with IRESSA when the adverse reaction fully resolves or improves to NCI CTCAE Grade 1.

Permanently discontinue IRESSA for:
- Confirmed interstitial lung disease (ILD) *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Severe hepatic impairment *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Gastrointestinal perforation *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Persistent ulcerative keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*

Dose Modifications for Drug Interactions

Strong CYP3A4 Inducers
Increase IRESSA to 500 mg daily in the absence of severe adverse drug reaction, and resume IRESSA at 250 mg seven days after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7)* and *Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)
ILD or ILD-like adverse drug reactions (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of the 2462 patients who received IRESSA across clinical trials; of these, 0.7% were Grade 3 or higher and 3 cases were fatal.

Withhold IRESSA and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. Permanently discontinue IRESSA if ILD is confirmed [*see Dosage and Administration (2.4) and Adverse Reactions (6.1) in the full Prescribing Information*].

Hepatotoxicity
In patients who received IRESSA across clinical trials, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Grade 3 or higher liver test abnormalities occurred in 5.1% (ALT), 3.0% (AST), and 0.7% (bilirubin) of patients. The incidence of fatal hepatotoxicity was 0.04%.

Obtain periodic liver function testing. Withhold IRESSA in patients with worsening liver function and discontinue in patients with severe hepatic impairment *[see Dosage and Administration (2.4), Adverse Reactions (6.1)*, and *Use in Specific Populations (8.7) in the full Prescribing Information]*.

Gastrointestinal Perforation
Gastrointestinal perforation occurred in three (0.1%) of the 2462 IRESSA-treated patients across clinical trials [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Permanently discontinue IRESSA in patients who develop gastrointestinal perforation [*see Dosage and Administration (2.4) in the full Prescribing Information*].

Severe or Persistent Diarrhea
Grade 3 or 4 diarrhea occurred in 3% of 2462 IRESSA-treated patients across clinical trials. Withhold IRESSA for severe or persistent (up to 14 days) diarrhea *[see Dosage and Administration (2.4)* and *Adverse Reactions (6.1) in the full Prescribing Information]*.

Ocular Disorders including Keratitis
Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blephritis and dry eye (6.7%)] occurred in the 2462 IRESSA-treated patients across clinical trials. The incidence of Grade 3 ocular disorders was 0.1% [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Interrupt or discontinue IRESSA for severe, or worsening ocular disorders [*see Dosage and Administration (2.4) in the full Prescribing Information*].

Bullous and Exfoliative Skin Disorders
Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme have been reported from treatment with IRESSA. Erythema multiforme and dermatitis bullous have been reported in two patients (0.08%) across NSCLC trials (Study 2, Study 3 and Study 4). IRESSA treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Embryo-fetal Toxicity
Based on its mechanism of action and data from animal reproduction studies IRESSA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy [*see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information*].

ADVERSE REACTIONS
The following adverse drug reactions are discussed in more detail in other sections of the labeling:
- Interstitial Lung Disease *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Hepatotoxicity *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Gastrointestinal Perforation *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Severe or Persistent Diarrhea *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Ocular Disorders including Keratitis *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Bullous and Exfoliative Skin Disorders *[see Warning and Precautions (5.6) in the full Prescribing Information]*

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

The safety of IRESSA is based on the data from 2462 patients with NSCLC who received IRESSA 250 mg daily monotherapy in three randomized clinical studies (Study 2, Study 3 and Study 4). Patients with a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis that required steroid treatment or any evidence of clinically active interstitial lung disease were excluded from these studies.

Controlled Studies:
Study 2 was a randomized, multicenter, open-label trial in which 1217 patients were randomized to receive first-line treatment for metastatic NSCLC; 607 patients received IRESSA 250 mg daily and 589 patients received carboplatin/paclitaxel. The median duration of treatment with IRESSA was 5.9 months. The study population characteristics were: median age 57 years, age less than 65 years (73%), female (79%), Asian (100%), NSCLC adenocarcinoma histology (100%), never smoker (94%), light ex-smoker (6%), ECOG PS 0 or 1 (90%).

Study 3 was a randomized, multicenter, double-blind, placebo-controlled trial in which 1692 patients were randomized to receive second- or third-line treatment for metastatic NSCLC; of which 1126 patients received IRESSA 250 mg daily and 562 patients received placebo. The median duration of treatment with IRESSA was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), Caucasian (75%), Asian (21%), NSCLC adenocarcinoma histology (48%), never smoker (22%), ECOG PS 0 or 1 (65%), PS 2 (29%), PS 3 (5%) and two or more prior therapies (51%).

Study 4 was a randomized, multicenter, open-label trial in which 1466 patients were randomized to receive second-line treatment for metastatic NSCLC; 729 patients received IRESSA 250 mg daily and 715 patients received docetaxel. The median duration of treatment with IRESSA was 2.4 months. The study population characteristics were: median age 61 years, age less than 65 years (61%), female (36%), Caucasian (79%), Asian (21%), NSCLC adenocarcinoma histology (54%), never smoker (20%), ECOG PS 0 or 1 (88%) and two or more prior therapies (16%).

The pooled safety database from the three randomized trials was used to evaluate for serious and uncommon adverse drug reactions. Common adverse reactions were evaluated in Study 3. The most frequent adverse reactions in Study 3 (incidence of >20% and greater than placebo) reported in IRESSA-treated patients were skin reactions (47%) and diarrhea (29%). The most frequent fatal adverse reactions in IRESSA-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

Approximately 5% of IRESSA-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

Table 1 – Selected Adverse Drug Reactions Occurring with an Incidence Rate ≥5% and an Increase of >2% of IRESSA-treated Patients in Study 3

	Percentage (%) of patients			
	IRESSA (N=1126)		Placebo (N=562)	
Adverse Reaction	**All Grades**	**Grade 3 and 4**	**All Grades**	**Grade 3 and 4**
Skin and subcutaneous tissue disorders				
Skin reactions[1]	47%	2%	17%	0.4%
Nail disorders[2]	5%	0.1%	0.7%	0%
Gastrointestinal disorders				
Diarrhea[3]	29%	3%	10%	1%
Vomiting	14%	1.2%	10%	0.4%
Stomatitis[4]	7%	0.3%	4%	0.2%
Metabolism and nutrition disorders				
Decreased appetite	17%	2.3%	14%	2.0%

ative atorvastatin administration did not affect any of these endpoints.

The safety analysis showed no indications of increased risk of skeletal muscle or liver injury with perioperative atorvastatin use.

In the real world, "Most patients presenting for cardiac surgery … are already taking statins, and in the current study there was little evidence that continuation or withdrawal from statin treatment on the day of surgery and postoperative day 1 affects AKI," wrote Dr. Billings and his coauthors.

Study limitations included its single-center design, and the use of AKI criteria that may not be sensitive to late-developing AKI. Also, for enrolled patients who were already on statins, statin exposure was not reduced in comparison with usual care.

The National Institutes of Health and the Vanderbilt University Medical Center department of anesthesiology funded the study. Dr. Brown reported receiving grants from Shire Pharmaceuticals and New Haven Pharmaceuticals, and personal fees from Novartis Pharmaceuticals and Alnylam Pharmaceuticals. The other authors reported no conflicts of interest.

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IRESSA® (gefitinib) tablets for oral use 2

Table 1 – Selected Adverse Drug Reactions Occurring with an Incidence Rate ≥5% and an Increase of >2% of IRESSA-treated Patients in Study 3 (cont'd.)

	Percentage (%) of patients			
	IRESSA (N=1126)		Placebo (N=562)	
Adverse Reaction	All Grades	Grade 3 and 4	All Grades	Grade 3 and 4
Eye disorders				
Conjunctivitis/blepharitis/dry eye[5]	6%	0%	3.2%	0%

[1] Includes Acne, Acne pustular, Dermatitis, Dermatitis acneiform, Dermatitis exfoliative, Drug eruption, Dry skin, Erythema, Exfoliative rash, Folliculitis, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin toxicity, Xeroderma
[2] Includes Ingrowing nail, Nail bed infection, Nail disorder, Nail infection, Onychoclasis, Onycholysis, Paronychia
[3] Includes Diarrhea, Feces soft, Frequent bowel movements
[4] Includes Aphthous stomatitis, Cheilitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral mucosal blistering, Stomatitis, Tongue disorder, Tongue ulceration
[5] Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Dry eye, Eye irritation, Eye pruritus, Eye swelling, Eyelid irritation, Eyelid edema, Eyelids pruritus

Table 2 – Treatment Emergent Laboratory Abnormalities Occurring More Frequently in IRESSA-Treated Patients in Study 3

	IRESSA		Placebo	
Adverse Reaction	All Grades %	Grade 3 and 4 %	All Grades %	Grade 3 and 4 %
Alanine aminotransferase increased[1]	38%[2]	2.4%	23%[2]	1.4%[4]
Aspartate aminotransferase increased[1]	40%[3]	2.0%	25%[3]	1.3%[5]
Proteinuria	35%	4.7%	31%	3.3%

[1] Patients were allowed to enter the clinical study with lab values of ALT or AST CTCAE grade 1 or 2
[2] 14% gefitinib patients and 10% placebo patients were CTC grade 1 or 2 ALT at baseline
[3] 15% gefitinib patients and 12% placebo patients were CTC grade 1 or 2 AST at baseline
[4] 0.2% of placebo patients were CTC grade 3 at baseline
[5] 0.4% of placebo patients were CTC grade 3 at baseline

The following adverse reactions have been reported with IRESSA across NSCLC trials (Study 2, Study 3 and Study 4) and are not listed elsewhere in Section 6: nausea (18%), asthenia (17%), pyrexia (9%), alopecia (4.7%), hemorrhage (including epistaxis and hematuria) (4.3%), dry mouth (2%), dehydration (1.8%), allergic reactions including angioedema and urticaria (1.1%), elevations in blood creatinine (1.5%), and pancreatitis (0.1%).

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of IRESSA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal and urinary disorders: cystitis, hemorrhagic cystitis

Skin and subcutaneous tissue disorders: cutaneous vasculitis

DRUG INTERACTIONS

Drugs Affecting Gefitinib Exposure

CYP3A4 Inducer
Drugs that are strong inducers of CYP3A4 increase the metabolism of gefitinib and decrease gefitinib plasma concentrations. Increase IRESSA to 500 mg daily in patients receiving a strong CYP3A4 inducer (e.g., rifampicin, phenytoin, or tricyclic antidepressant) and resume IRESSA at 250 mg 7 days after discontinuation of the strong inducer [*see Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3) in the full Prescribing Information*].

CYP3A4 Inhibitor
Drugs that are strong inhibitors of CYP3A4 (e.g., ketoconazole and itraconazole) decrease gefitinib metabolism and increase gefitinib plasma concentrations. Monitor adverse reactions when administering strong CYP3A4 inhibitors with IRESSA.

Drugs Affecting Gastric pH
Drugs that elevate gastric pH (e.g., proton pump inhibitors, histamine H_2-receptor antagonists, and antacids) may reduce plasma concentrations of gefitinib. Avoid concomitant use of IRESSA with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, take IRESSA 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Take IRESSA 6 hours after or 6 hours before an H_2-receptor antagonist or an antacid [*see Clinical Pharmacology (12.3) in the full Prescribing Information*].

Hemorrhage in Patients taking Warfarin
International Normalized Ratio (INR) elevations and/or hemorrhage have been reported in some patients taking warfarin while on IRESSA therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and animal data, IRESSA can cause fetal harm when administered to a pregnant woman. In animal reproductive studies, oral administration of gefitinib from organogenesis through weaning resulted in fetotoxicity and neonatal death at doses below the recommended human dose (*see Animal Data*). Advise pregnant women of the potential hazard to a fetus or potential risk for loss of the pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data
A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m^2, about 0.2 times the recommended human dose on a mg/m^2 basis). When pregnant rats were treated with 5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg (approximate the human clinical dose on a mg/m^2 basis) and was accompanied by high neonatal mortality soon after parturition. In rabbits, a dose of 20 mg/kg/day (240 mg/m^2, about twice the recommended dose in humans on a mg/m^2 basis) caused reduced fetal weight.

Lactation

Risk Summary

It is not known whether IRESSA is excreted in human milk. Animal studies indicate the gefitinib and its metabolites are present in rat milk at a concentration higher than those in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from IRESSA, advise women to discontinue breast-feeding during treatment with IRESSA.

Data

Animal Data
Levels of gefitinib and its metabolites were 11-to-19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action and animal data, IRESSA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1) in the full Prescribing Information*]. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy.

Infertility

IRESSA may result in reduced fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

Pediatric Use
The safety and effectiveness of IRESSA in pediatric patients have not been established.

Geriatric Use
Of the 823 patients enrolled in two randomized, active-controlled clinical trials 374 patients (45%) were 65 years and older, and 93 patients (11%) were 75 years and older. No overall differences in safety were observed between patients 65 years and older and those younger than 65 years. There is insufficient information to assess for differences in efficacy between older and younger patients.

Renal Impairment
Less than four percent (<4%) of gefitinib and its metabolites are excreted via the kidney. No clinical studies were conducted with IRESSA in patients with severe renal impairment.

Hepatic Impairment
The systemic exposure of gefitinib was compared in patients with mild, moderate, or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification) and healthy subjects with normal hepatic function (N=10/group). The mean systemic exposure ($AUC_{0-\infty}$) was increased by 40% in patients with mild impairment, 263% in patients with moderate impairment, and 166% in patients with severe hepatic impairment. Monitor adverse reactions when IRESSA is administered to patients with moderate and severe hepatic impairment.

In a study comparing 13 patients with liver metastases and moderate hepatic impairment (addition of CTC grade of baseline AST/SGOT, ALP, and bilirubin equals 3 to 5) to 14 patients with liver metastases and normal hepatic function, the systemic exposure of gefitinib was similar [*see Warnings and Precautions (5.2) in the full Prescribing Information*].

OVERDOSAGE
Twenty three patients were treated weekly with doses from 1500 mg to 3500 mg, and IRESSA exposure did not increase with increasing dose. Adverse events were mostly mild to moderate in severity, and were consistent with the known safety profile of IRESSA. In the event of suspected overdose, interrupt IRESSA, institute supportive care, and observe until clinical stabilization. There are no specific measures/treatments that should be taken following IRESSA overdosing.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labelling (Patient Information).

Interstitial Lung Disease: Advise patients to immediately contact their healthcare provider for new onset or worsening of pulmonary symptoms such as dyspnea, cough and fever [*see Warnings and Precautions (5.1) in the full Prescribing Information*].

Hepatotoxicity: Inform patients that they will need to undergo lab tests to monitor for liver function. Advise patients to contact their healthcare provider to report any new symptoms indicating hepatic toxicity [*see Warnings and Precautions (5.2) in the full Prescribing Information*].

Gastrointestinal Perforation: Advise patients that IRESSA can increase the risk of gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain [*see Warnings and Precautions (5.3) in the full Prescribing Information*].

Severe or Persistent Diarrhea: Advise patients to contact their healthcare provider for severe or persistent diarrhea [*see Warnings and Precautions (5.4) in the full Prescribing Information*].

Ocular Disorders including Keratitis: Advise patients promptly to contact their healthcare provider if they develop eye symptoms, lacrimation, light sensitivity, blurred vision, eye pain, red eye or changes in vision *[see Warnings and Precautions (5.5) in the full Prescribing Information].*

Bullous and Exfoliative Skin Disorders: Advise patients that IRESSA can increase the risk of bullous and exfoliative skin disorders and to seek immediately medical attention for severe skin reactions [*see Warnings and Precautions (5.6) in the full Prescribing Information*].

Embryo-fetal Toxicity: Advise pregnant women of the potential risk to a fetus or potential risk for loss of the pregnancy [*see Warnings and Precautions (5.7) and Use in Specific Populations (8.1) in the full Prescribing Information*]. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy [*see Use in Specific Populations (8.3) in the full Prescribing Information*].

Lactation: Advise women to discontinue breast-feeding during treatment with IRESSA [*see Use in Specific Populations (8.2) in the full Prescribing Information].*

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FDA approves new anthrax treatment

BY RICHARD PIZZI
Frontline Medical News

The Food and Drug Administration has approved Anthim (obiltoxaximab) injection to treat inhalational anthrax, in combination with appropriate antibacterial drugs.

Anthim is a monoclonal antibody that neutralizes toxins produced by the bacterium *Bacillus anthracis*. Anthim was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. When alternative therapies are not available or not appropriate, anthim can be used to prevent inhalational anthrax, a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores.

The drug was developed by Elusys Therapeutics Inc. of Pine Brook, N.J., in conjunction with the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority.

Anthim's effectiveness was demonstrated in studies conducted in animals based on survival at the end of the studies. More animals treated with Anthim lived, compared with animals treated with placebo. Anthim administered in combination with antibacterial drugs resulted in higher survival outcomes than antibacterial therapy alone.

The safety of Anthim was evaluated in 320 healthy human volunteers. The most frequently reported side effects were headache, itching (pruritus), upper respiratory tract infections, cough, nasal congestion, hives, and bruising, swelling and pain at the infusion site.

For more information, see the FDA's approval announcement.

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CPAP extended BP-lowering impact of losartan

BY CHRISTINE KILGORE
Frontline Medical News

In patients with new-onset hypertension and obstructive sleep apnea, continuous positive airway pressure (CPAP) therapy plus antihypertensive treatment with losartan led to reductions in systolic blood pressure beyond those achieved with losartan alone, a two-phase study found.

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"Adding CPAP treatment to losartan may reduce blood pressure in a clinically relevant way if the patients are compliant with the device," said Dr. Erik Thunström of the Sahlgrenska Academy at the University of Gothenburg, Sweden, and his associates. If using CPAP with losartan has an additive blood pressure-lowering effect, it "favors the idea that it contributes to a further down-regulation of RAAS [renin-angiotensin-aldosterone system] activity in new-onset hypertension and OSA".

In their open-label study, 89 men and women with new-onset untreated hypertension – 54 of whom were found to have obstructive sleep apnea (OSA) through a home sleep study and 35 of whom were determined to not have OSA – were treated for 6 weeks with losartan, 50 mg daily. Ambulatory 24-hour blood pressure monitoring was performed before and after treatment.

The patients with OSA were then randomized to receive 6 weeks of nightly add-on CPAP therapy or to continue losartan alone. Ambulatory 24-hour blood pressure monitoring was performed again.

Losartan alone reduced blood pressure in patients with hypertension and concomitant OSA, but the effect was smaller than that seen in patients without OSA. Statistically significant differences were seen in the mean net reduction in morning systolic blood pressure and morning mean arterial pressure.

After 6 weeks of losartan alone, a blood pressure less than 130/80 mm Hg was achieved by 12.5% of the patients with OSA and by 29% of the patients without OSA.

After 6 weeks of add-on CPAP therapy, 25% of patients with OSA achieved blood pressures less than 130/80 mm Hg. The differences in blood pressures for the OSA patients receiving CPAP plus losartan and those receiving losartan alone were 4.4 mm Hg for 24-hour systolic blood pressure, 1.9 mm Hg for diastolic, and 2.5 mm Hg for mean arterial pressure.

The most "robust" blood pressure changes were seen in the patients who used CPAP therapy for more than 4 hours every night, reducing the mean 24-hour systolic blood pressure by 6.5 mm Hg, the diastolic pressure by 3.8 mm Hg, and the mean arterial blood pressure by 4.6 mm Hg, the researchers reported (Am J Respir Crit Care Med. 2016 Feb.;193:310-20). "Adding CPAP to treatment with losartan reduced the mean 24-hour systolic blood pressure by 6.5 mm Hg in the subgroup of patients with OSA who were adherent with CPAP," they wrote.

VIEW ON THE NEWS

Dr. David Schulman, FCCP, comments: The relationship between sleep apnea and hypertension (both prevalent and incident) has been well described for many years. It is not entirely clear, however, that treatment of obstructive sleep apnea can lead to a meaningful decrease in blood pressure. Although relatively small, this study by Thunstrom et al sheds some additional light on the association. Patients with hypertension and comorbid obstructive sleep apnea (OSA) were less likely to show a meaningful response to antihypertensives than those without concomitant sleep-disordered breathing. In the subgroup with OSA that was randomized to subsequent administration of CPAP, blood pressure dropped more than it did with antihypertensive alone, albeit by only 4 mm Hg (and slightly more in the highly CPAP adherent subjects).

There are a couple of interesting features regarding subject enrollment that are worthy of mention. First, the study was restricted to individuals with a body mass index below 35, potentially limiting generalizability of the findings to a more obese population. Importantly, though, all subjects were screened for OSA, independent of sleepiness, suggesting that the findings may be extrapolated to non-sleepy apneics, a population that we are probably not as aggressive about identifying.

Will this manuscript change current practice? Probably not. But it may offer some insight into the mechanism by which sleep apnea increases blood pressure. And if it leads more providers to screen even their non-sleepy hypertensives for sleep-disordered breathing in the hope of improving future cardiovascular risk, that would be a breath of fresh air.

Sleep apnea found in 57% of veterans with PTSD

BY CHRISTINE KILGORE
Frontline Medical News

FROM CHEST

Obstructive sleep apnea syndrome (OSAS) was diagnosed in more than half of 200 active duty service members with combat-related post-traumatic stress disorder (PTSD) who were studied at Walter Reed Army Medical Center in Washington.

Compared with age-matched peers with just one of these disorders, the service members with PTSD and OSAS had poorer somnolence and sleep-related quality of life and were less adherent and responsive to positive airway pressure therapy.

The findings "highlight the need for a high index of suspicion and a comprehensive approach to identifying and treating sleep-disordered breathing in these patients," Dr. Christopher J. Lettieri of the Uniformed Services University in Bethesda, Md., and his associates wrote (Chest. 2016 Feb;149[2]:483-90). "Given the prevalence of OSAS in patients with PTSD and its adverse impact on symptoms and adherence, early identification may improve outcomes."

In the observational cohort study, 200 consecutive active duty service members who were diagnosed with PTSD as part of post-deployment screening underwent sleep evaluations regardless of whether there was clinical suspicion of sleep-disordered breathing. More than half – about 57% – were diagnosed with OSAS. Almost 60% of the study group had mild traumatic brain injury, which has been connected in prior research to obstructive sleep apnea, and many had comorbid insomnia. Those who were diagnosed with OSAS were older and had higher BMIs than those not found to have OSAS.

All 200 patients were compared with 50 consecutive age-matched control patients who had OSAS but had not been deployed and did not have PTSD, as well as with 50 age-matched service members without prior deployment or either of the two disorders. All of the patients diagnosed with OSAS were prescribed positive airway pressure (PAP) therapy and evaluated after a month.

Sleep quality was poor in the majority of patients with PTSD, and OSAS and PTSD were both independently associated with increased daytime sleepiness and lower quality-of-life index scores. However, patients with both conditions fared significantly worse, particularly with respect to quality of life as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ). FOSQ scores were abnormal at baseline in 60% of those with PTSD and OSAS, 43% with PTSD alone, 24% with OSAS alone, and 7% of those with neither condition.

While continuous PAP therapy improved daytime sleepiness and quality of life in patients with both PTSD and OSAS, the degree of improvement was less than that experienced by those with OSAS alone. PTSD "represents an independent barrier to the effective treatment of OSAS and should prompt multipronged and individualized care," they wrote.

The researchers reported having no financial disclosures.

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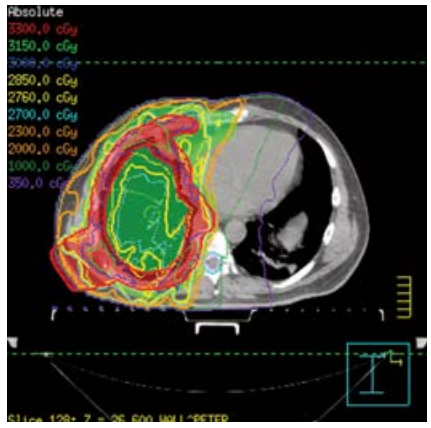
Preop radiation boosts extrapleural pneumonectomy

BY RICHARD MARK KIRKNER
Frontline Medical News

The popularity of extrapleural pneumonectomy to treat asbestos-related thoracic mesothelioma has yielded to extended pleurectomy/decortication in recent years, but a study suggests that the extrapleural pneumonectomy procedure can achieve good results in a new protocol that involves administering radiation therapy before surgery as opposed to the more conventional approach of radiation after surgery.



Researchers at the University of Toronto reported on their protocol that uses accelerated intensity modulated radiation therapy (IMRT) for malignant pleural mesothelioma (MPM) (J Thorac Cardiovasc Surg. doi: 10.1016/j.jtcvs.2015.09.129). They call the protocol SMART, for Surgery for Mesothelioma After Radiation Therapy.

"The rationale to develop this protocol was to optimize the delivery of radiation to the whole tumor bed, sterilize the edges of the tumor to limit the risk of spillage at the time of surgery, develop a shorter treatment plan and potentiate the activation of the immune system by using a hypofractionated regimen," wrote Dr. Marc de Perrot and colleagues.

The protocol involves delivering 25 Gy of radiation in five daily fractions over a week to the entire side of the thorax with 5 Gy boosts based on imaging, followed by extrapleural pneumonectomy (EPP) 4-6 days later. Patients with three or more positive lymph notes (ypN2 disease) also are offered adjuvant chemotherapy.

The researchers performed the protocol on 62 patients from November 2008 to October 2014, which represents 24% of all patients with MPM seen at the institution in that period. Fifty-two patients were men and ages ranged from 41 to 75 years. Clinical stage of cancer ranged from T1N0 in 10 patients, to T2N0 in 35 and T3N0 in 13 (two had T4N0 and two had T3N2). Forty-five had right-side cancers. Six patients received an extended protocol for various reasons, including tumor extending to the chest wall.

All 62 patients completed IMRT and EPP. All but one had resection and reconstruction of the diaphragm, and all but four had resection and reconstruction of the pericardium.

Overall death rate was 4.8% (three patients). Results were better in patients with epithelioid tumors, with a median survival of 51 months and disease-free survival of 47 months. Those with biphasic subtypes had median survival of 10 months and disease-free survival of 8 months. Eight patients had ipsilateral chest recurrence. "This analysis demonstrates that the SMART approach is particularly encouraging for patients with epithelial subtype," Dr. de Perrot and coauthors said. They no longer perform the SMART protocol on patients with biphasic subtype.

The protocol was not without complications. Twenty-four patients, about 38%, had serious complications that required intervention or worse. Twelve had atrial fibrillation, but none advanced to life-threatening disease. Among other complications, four had empyema – one resulting in death – and three had pulmonary emboli. One other patient in the complications group died from pneumonia, and another died from a heart attack at home.

This is the Toronto researchers' second attempt at studying the three-modality approach. In their first attempt, only half the patients who started with preoperative chemotherapy went onto complete the radiation after surgery because of difficulties administering it (J Thorac Cardiovasc Surg. 2007;133:111-6; J Clin Oncol. 2009;27:1413-8). Also, about 25% of patients had disease progression during induction chemotherapy and could not go onto surgery.

The study authors had no conflicts to disclose.

VIEW ON THE NEWS

Results hard to reproduce

Implementing the treatment regimen for malignant pleural mesothelioma (MPM) that the Toronto researchers studied poses several high stakes challenges and will be difficult to replicate. The study results are among the best reported for MPM to date, but are they solely related to patient selection or do they reflect the true impact of a novel approach to treatment?

Patients selected for the treatment need to be able to undergo the extrapleural pneumonectomy and the surgeon has to be able to predict the resectability of the tumor. But limitations in existing staging methods for MPM make it difficult to predict tumor resectability. To avoid bronchial stump leaks and other serious complications requires experience along with meticulous surgical technique and postoperative care. Only high-volume centers of excellence could potentially reproduce these results.

Despite the waning in popularity of EPP, the study results underscore its effectiveness in carefully selected patients – those with epithelioid tumor histology and no tumor metastases.

Dr. Valerie Rusch, FCCP, and coauthors at Memorial Sloan-Kettering Cancer Center, New York, made these remarks in a commentary (J Thorac Cardiovasc Surg. doi: 10.1016/j.jtcvs.2015.10.038) accompanying the editorial.

Certain cancers raise the risk for subsequent NSCLC

BY DOUG BRUNK
Frontline Medical News

PHOENIX – A history of head and neck, lung, bladder, and hematologic malignancies was associated with an increased rate of subsequent non–small cell lung cancer (NSCLC), a large analysis of national data found.

"It is unclear to what extent the higher rate of primary NSCLC in these patients may be attributed to smoking, previous cancer history, or other lung cancer risk factors," researchers led by Dr. Geena Wu wrote in an abstract presented during a poster session at the annual meeting of the Society of Thoracic Surgeons. "Further research using individual smoking data may better delineate who is at increased risk of NSCLC based on prior cancer site and smoking history."

In a study that Dr. Wu led during a research fellowship at the City of Hope National Medical Center, Duarte, Calif., she and her associates used the Surveillance, Epidemiology, and End Results (SEER) 1992-2007 dataset to identify 32,058 patients with a prior malignancy who subsequently developed primary lung cancer at 6 months or more after their initial cancer. They calculated standardized incidence ratios (SIRs) for NSCLC as a rate of observed to expected NSCLC cases adjusted by person-years at risk, age, gender, and time of diagnosis.

The researchers found that patients with a history of the following cancers had higher rates of second primary NSCLC than expected: head and neck (SIR, 4.00), colon and rectum (SIR, 1.16), pancreas (SIR, 1.44), lung (SIR, 4.88), bladder (SIR, 1.97), kidney (SIR, 1.21), breast (SIR, 1.09), and leukemia or lymphoma (SIR, 1.40).

At the same time, patients with a history of pancreatic or breast cancer who were treated with radiation had a higher incidence of second primary NSCLC (SIR of 2.54 and SIR of 1.14, respectively), while those who were not treated with radiation did not.

"Just because someone has a previous history of cancer, they're not necessarily at increased risk of a second lung cancer," Dr. Wu, who is now a fourth-year general surgery resident at Maricopa County Hospital in Phoenix said in an interview at the meeting. "You have to look at what kind of cancer they had and what their smoking history is – whether or not they continue to smoke, because smoking is such an important risk factor."

The SEER database does not contain information about patient smoking history. It also lacks details about the type of chemotherapy patients receive, "so whether or not chemotherapy plays an impact in the elevated risk of lung cancer we can't say."

Dr. Wu reported having no financial disclosures.

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SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Strong Dual Inhibitors of CYP3A4 and P-gp:** Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.
- **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

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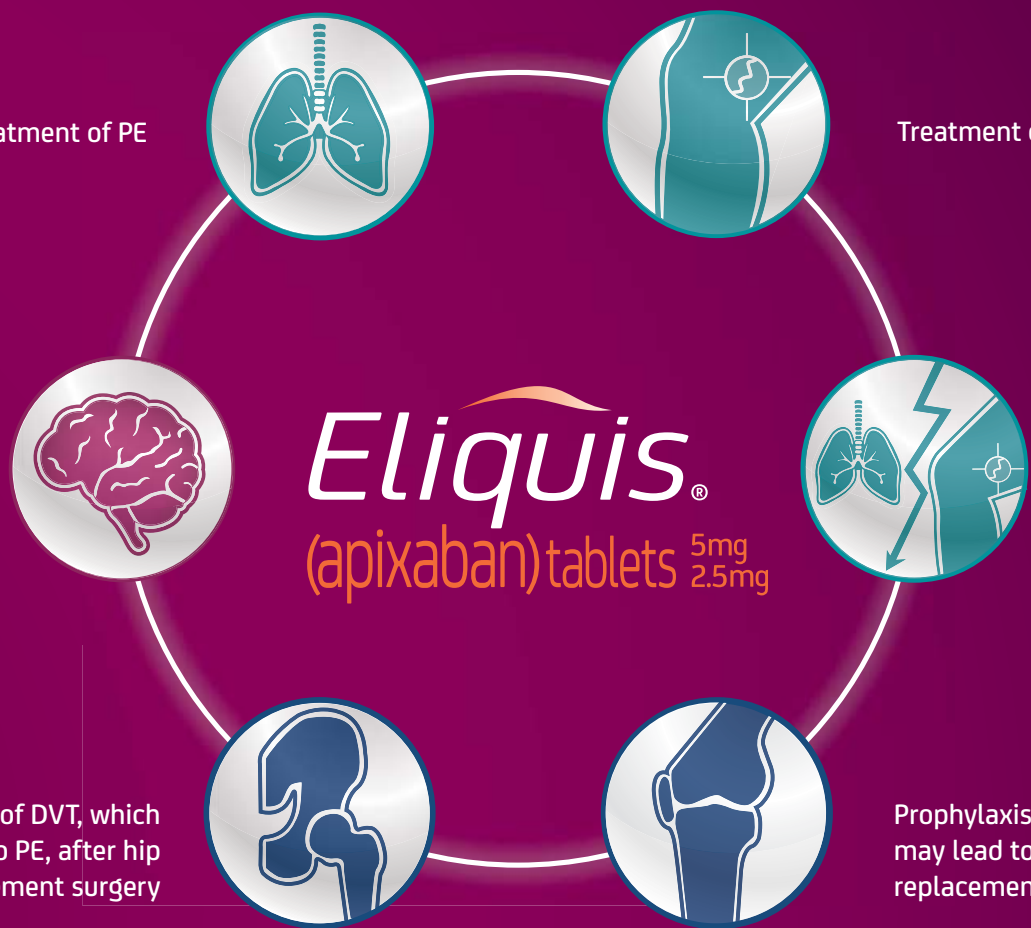
Approved for 6 indications



Learn more about ELIQUIS for the treatment of DVT/PE and access reprints of our clinical studies.

hcp.eliquis.com

NVAF=nonvalvular atrial fibrillation; DVT=deep vein thrombosis; PE=pulmonary embolism.

SELECTED IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS (CONT'D)

- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNINGS, on the adjacent pages.

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery—ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS (apixaban). The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions]*

Clinical Trials Experience

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

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment *[see Dosage and Administration (2.1) in full Prescribing Information]*. Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

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Infectious disease hospitalizations on the decline

BY TARA HAELLE
Frontline Medical News

The rate of pediatric hospitalizations for infectious diseases has decreased overall among U.S. children from 2000 to 2012, though skin infection hospitalizations have climbed, a recent study found.

"The observed reduction in infectious disease hospitalizations (vaccine-preventable diseases and others) supports a cautious optimism that the infectious disease-related morbidity can be further reduced," Dr. Tadahiro Goto of the department of emergency medicine at Massachusetts General Hospital, Boston, and coauthors reported online.

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Yet approximately 625,000 children were still hospitalized for infectious diseases in 2012. "These findings should facilitate continued efforts, such as bridging the gaps in immunization coverage, to reduce the infectious disease–related morbidity and health care utilization nationally," the authors wrote (Pediatr Infect Dis J. 2016 Mar 10. doi: 10.1097/INF.0000000000001134).

The researchers analyzed all cases of youth under age 20 years with an infectious disease diagnosis who were included in the nationally representative Kids' Inpatient Database for 2000, 2003, 2006, 2009 and 2012.

In their cross-sectional analysis, the authors identified more than 2.2 million pediatric infectious disease hospitalizations, which translated to a weighted estimate of nearly 3.7 million across the five datasets. These hospitalizations comprised almost a quarter (24.5%) of all pediatric hospitalizations over those 12 years, but their rate dropped 16.5%, from 91/10,000 children in 2000 to 75.8/10,000 children in 2012 (*P* less than .001). A 30.3% decrease in hospitalizations among infants less than 1 year old primarily drove the overall rate decline, alongside a slighter (13.4%) drop in children aged 1-4 years.

Lower respiratory infections, including pneumonia and bronchiolitis, were the most common infectious diseases leading to pediatric hospitalization. Although these accounted for 42.8% of all infectious disease hospitalizations in 2012, their hospitalization rate had dropped 19.1% since 2000, from 40.1 children to 32.5 children per 10,000, driven mostly by a 25.5% drop in pneumonia hospitalizations.

Abdominal and rectal infections comprised 13.8% of all infectious disease hospitalizations in 2012 but had declined 6.9% since 2000. Upper respiratory infections had been the third most common subgroup in 2000 but was replaced by skin infections in 2012.

Hospitalization rates decreased for all infectious disease subgroups except skin infections, perinatal infections, septicemia, and postoperative infections. Skin infections had the biggest jump, 67.6% over the period studied (*P* less than .001), followed by a 16.7% increase in perinatal infections and smaller increases in the other two subgroups.

The biggest subgroup declines were HIV/AIDS, with an 81.5% drop, and nonviral meningitis, with a 64.9% drop. Mortality in the hospital also declined among children admitted for infectious disease: those admitted in 2012 had 37% reduced odds of death, compared with those admitted in 2000.

The median length of a hospital stay, 2 days, did not change across time, and the median cost for each hospitalization increased 9.6%, from $3,452 in 2003 to $3,784 in 2012. Nationwide, however, infectious disease hospitalizations cost $4.4 billion in 2012.

The research was funded by the National Institutes of Health. Information on disclosures was not provided.

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Readmissions drop with asthma meds at discharge

BY AMY KARON
Frontline Medical News

A bedside medication delivery service increased the percentage of asthma patients discharged with medications in hand from 0% to 75%, which helped prevent emergency department readmissions within the next month, according to an exploratory, retrospective analysis.

"To our knowledge this report is the first to detail specific strategies to reliably discharge patients with meds in hand," said Dr. Jonathan Hatoun of Boston University Medical Center and his associates.

Before the intervention, the hospital previously had routinely discharged asthma patients without medications in hand, and in 2011, a survey showed that 37% never filled their prescriptions. Concerned that patients were "unnecessarily suffering," Dr. Hatoun and his associates assembled a multidisciplinary team that worked for 2 years to improve this outcome measure. They initially asked residents to write prescriptions at least a day before discharge, but they were concerned that treatment plans could change. Next, they asked families to pick up medications at the hospital pharmacy, but parents were reluctant to leave their sick child's bedside. Therefore, the researchers designed an in-room service in which pharmacists delivered the medications to the child's room when a parent was present (Pediatrics 2016 Feb 24. doi: 10.1542/peds.2015-0461).

"Copayments were collected in the room, either in cash or with a mobile credit payment system purchased by the pharmacy," the researchers explained. "Unlike traditional pharmacy pickup, the delivery service allows the patient, parent, nurse, and pharmacist to be together in the patient's hospital room for teaching with the actual medications available for demonstration."

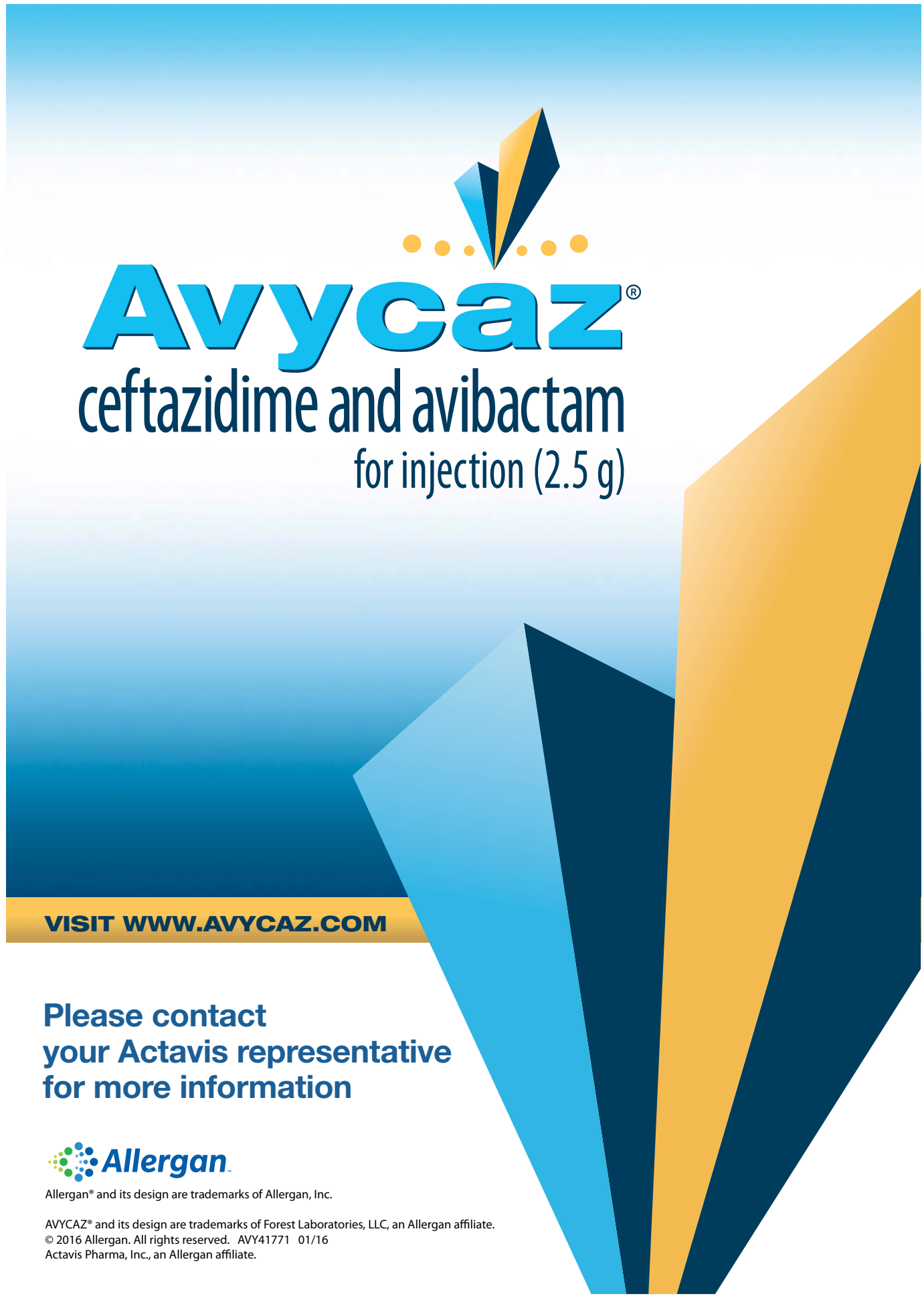
The delivery service not only met the project goal to increase the "meds in hand" rate from 0% to 75%, but an analysis of patients with complete insurance claims showed that patients discharged with medications in hand were significantly less likely to return to the emergency department within 30 days of discharge, for any reason, compared with patients who received usual care (odds ratio, 0.22; 95% confidence interval, 0.05-0.99).

"[M]ore evidence on the impact of being discharged in possession of discharge medications is needed ...," " the investigators noted. "Additional areas of exploration could include how the Meds-in-Hand service affects the patient experience, hospital finances, and clinical outcomes for other medical conditions."

The authors had no external funding sources or disclosures.

VIEW ON THE NEWS

Dr. Susan Millard, FCCP, comments: The researchers from Boston University Medical Center have developed an out of the box approach to help families during stressful hospitalizations. The result is that the patients also benefit in the long run!



Early peanut consumption protects from allergy

BY BRUCE JANCIN
Frontline Medical News

LOS ANGELES – A peanut allergy prevention strategy based upon regular consumption of peanut-containing foods from infancy to age 5 continued to provide protection even after peanut intake was halted for a full year from age 5 to 6, according to new results from an extension of the landmark LEAP trial, known as LEAP-On, presented at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The impetus for LEAP-On was the investigators' concern that a period of peanut avoidance might cause loss of the protective state. But that didn't occur.

Peanut allergy was prevented in 6-year-olds. What remains to be seen is if the protection will continue.

DR. LACK

"I think there is no doubt that we have prevented peanut allergy so far in these high-risk children. Next, the LEAP-Ad Lib study will tell us whether we've prevented it by age 10," said Dr. Gideon Lack of King's College London, who headed LEAP-On.

A second major randomized trial known as EAT (Enquiring About Tolerance) presented at the meeting provided further support for early dietary introduction of allergenic foods. EAT differed from LEAP (Learning Early About Peanut Allergy) and LEAP-On in that it ambitiously randomized infants to early introduction or avoidance of not one but six allergenic foods: peanut, cooked egg, cow's milk, fish, sesame, and wheat. Also, while LEAP and LEAP-On involved roughly 600 infants known to be at very high risk for allergy, EAT was conducted in a general population of 1,303 infants who weren't at increased risk, all of whom were exclusively breast-fed until the intervention beginning at age 3 months.

The presentation of the LEAP-On and EAT results at the AAAAI annual meeting was a major event marked by the National Institute of Allergy and Infectious Diseases by same-day release of new NIAID-sponsored draft recommendations for the diagnosis and management of food allergies.

In a press conference held at the AAAAI annual meeting to announce the start of a 45-day public comment period for the draft update of the 2010 guidelines, Dr. Daniel Rotrosen, director of NIAID's division of allergy, immunology and transplantation, said the new guidelines were developed largely in response to the compelling LEAP findings. That trial demonstrated that sustained consumption of peanut starting in infancy resulted in an 81% lower rate of peanut allergy at age 5 years compared to a strategy of peanut avoidance (N Engl J Med. 2015;372:803-13).

The draft guidelines, now available

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity

FOR PULMONARY ARTERIAL HYPERTENSION

ORENITRAM DOSING ADAPTS

Introduce prostacyclin treatment early with Orenitram, which enables you to adjust dose based on tolerability and clinical response.

The only prostacyclin analogue in a tablet:

For PAH, a **progressive disease**[1-3]

Early use in FC II and III[1]

Ability to **transition from treprostinil** parenteral therapy[1]*

Orenitram allows you to initiate treatment with 0.125 mg TID (~8 hrs apart) or 0.25 mg BID (~12 hrs apart), then titrate up or down every 3 to 4 days as needed per Full Prescribing Information (PI). In the pivotal trial, dose was titrated based on clinical response and tolerability. If not tolerated, titrate slower or decrease dose by 0.25 mg. Avoid abrupt discontinuation. Orenitram tablets should be taken whole and with food. If a dose is missed, please refer to the PI. Orenitram should not be used in patients with moderate hepatic impairment. Dose adjustments required for mild hepatic impairment.

*In a 24-week, multicenter, open-label study to establish safety and tolerability of transition, WHO Group 1 patients (FC I or II) on stable doses of IV/SC treprostinil as well as a PDE-5i and/or ERA were evaluated.

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"I expect the new guidelines, when finalized, to be endorsed by the leadership of all the participating organizations."

DR. ROTROSEN

on the NIAID website, represent a sharp departure from the former recommendation that physicians encourage exclusive breastfeeding for the first 6 months of life followed by cautious introduction of other foods. Whereas the former orthodoxy was that delayed introduction of allergenic foods protects against development of food allergy, the new evidence-based concept supported by the LEAP and EAT findings is that just the opposite is true: that is, introduction of such foods during the period of immunologic plasticity in infancy induces tolerance.

Thus, the draft guidelines recom-

Continued on following page

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INDICATION

Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

IMPORTANT SAFETY INFORMATION FOR ORENITRAM

CONTRAINDICATIONS

- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
- Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
- Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans
- It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding
- Safety and effectiveness in patients under 18 years of age have not been established
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

ADVERSE REACTIONS

- In the 12-week placebo-controlled monotherapy study, adverse reactions that occurred at rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

OREISIhcpJAN16

Please see the Brief Summary of the Full Prescribing Information for Orenitram on the following page.
For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

orenitram®
treprostinil
EXTENDED-RELEASE TABLETS
dosing that adapts.

References: 1. Orenitram [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2016. **2.** Clapp LH, Gurung R. The mechanistic basis of prostacyclin and its stable analogues in pulmonary arterial hypertension: role of membrane versus nuclear receptors. *Prostaglandins Other Lipid Mediat*. 2015;120:56-71. **3.** McLaughlin VV et al. ACCF/AHA 2009 expert consensus on pulmonary hypertension: developed in collaboration with the ACCP, ATS, and the PHA. *Circulation*. 2009;119(16):2250-2290.

Continued from previous page

mend that infants at high risk for peanut allergy because they have severe eczema and/or egg allergy should have introduction of peanut-containing food at 4-6 months of age to reduce their risk of peanut allergy, preceded by evaluation using peanut-specific IgE or skin prick testing to make sure it's safe. That age window coincides with well-child visits and vaccination schedules, Dr. Rotrosen noted.

These guidelines represent the consensus of 26 organizations that participated in their development. Among them are the American Academy of Pediatrics, the American Academy of Family Physicians, the American Academy of Dermatology, the American College of Gastroenterology, and AAAAI.

"I expect the new guidelines, when finalized, to be endorsed by the leadership of all the participating organizations," Dr. Rotrosen said.

The new paradigm will require cultural change, said Dr. James R. Baker Jr., CEO and chief medical officer of Food Allergy Research and Education, a nonprofit organization that provided partial funding for LEAP and LEAP-On.

"I think for a long time we've vilified these foods. There's nothing inherently wrong with their intake, and that's a message we need to get across to parents and physicians so they can start thinking differently," he said.

"The good news about these studies is that they show there's no reason not to do this," Dr. Baker added.

"There's no harm that comes from the early introduction [of potential allergens, like peanuts]."

DR. BAKER

"There's no harm that comes from the early introduction."

Dr. Lack, who led the EAT trial, noted that the study didn't meet it's primary endpoint of a significantly lower prevalence of food allergy to any of the six intervention foods at age 3 years in the intention-to-treat analysis. But adherence to the demanding EAT early-introduction protocol was a problem. Indeed, only 43% of participants adhered to the study protocol. In a per-protocol analysis restricted to the adherent group, however, early introduction was associated with a highly significant 67% reduction in the relative risk of food allergy at 3 years of age compared to controls. And for the two most prevalent food allergies – to peanut and egg – the relative risk reductions in the early-introduction group were 100% and 75%, respectively.

The EAT results suggest that an effective preventive dose of peanut in infants at least 3 months of age is roughly 2 g of peanut protein per week, equivalent to just under 2 tsp of peanut butter, according to Dr. Lack.

Simultaneously with presentation of the LEAP-On and EAT trials in Los Angeles, the studies were published online at NEJM.org (doi: 10.1056/NEJMoa1514210 for LEAP-ON and 10.1056/NEJMoa1514209 for EAT).

LEAP-On was supported primarily by NIAID. EAT was funded mainly by the UK Foods Standards Agency and the Medical Research Council. Dr. Lack reported receiving grants from those agencies as well as Food Allergy Research and Education.

bjancin@frontlinemedcom.com

orenitram®
treprostinil
EXTENDED-RELEASE TABLETS

BRIEF SUMMARY

The following is a brief summary of the full prescribing information for Orenitram® (treprostinil) Extended-Release Tablets. Please review the full prescribing information before prescribing Orenitram.

INDICATIONS AND USAGE

Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

CONTRAINDICATIONS

Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS

Worsening PAH Symptoms upon Abrupt Withdrawal—Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

Risk of Bleeding—Orenitram inhibits platelet aggregation and increases the risk of bleeding.

Use in Patients with Blind-end Pouches—The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

ADVERSE REACTIONS

Clinical Trials Experience—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included: headache, diarrhea, nausea and flushing. Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least a year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

	Treatment (%)	
Reaction	**Orenitram (N=151)**	**Placebo (N=77)**
Headache	63%	19%
Diarrhea	30%	16%
Nausea	30%	18%
Flushing	15%	6%
Pain in jaw	11%	4%
Pain in extremity	14%	8%
Hypokalemia	9%	3%
Abdominal discomfort	6%	0%

The safety of Orenitram was also evaluated in an open-label study transitioning patients from Remodulin. The safety profile during this study was similar to that observed in the three pivotal studies.

DRUG INTERACTIONS

Antihypertensive Agents or Other Vasodilator—Concomitant administration of Orenitram with diuretics, antihypertensive agents or other vasodilators increases the risk of symptomatic hypotension.

Anticoagulants—Treprostinil inhibits platelet aggregation; there is increased risk of bleeding, particularly among patients receiving anticoagulants.

Effect of CYP2C8 Inhibitors—Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil in healthy adult volunteers increases exposure to treprostinil. Reduce the starting dose of Orenitram to 0.125 mg BID and use 0.125 mg BID increments every 3 to 4 days.

Effect of Other Drugs on Orenitram—Based on human pharmacokinetic studies, no dose adjustment of Orenitram is recommended when coadministered with either fluconazole, rifampin, sildenafil, bosentan, or esomeprazole.

Warfarin—A drug interaction study was carried out with Remodulin co-administered with warfarin (25 mg/day) in healthy volunteers. There was no clinically significant effect of either medication on the pharmacokinetics of treprostinil. Additionally, treprostinil did not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the international normalized ratio (INR) in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—*Pregnancy Category C*. Animal reproductive studies with treprostinil diolamine have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans.

Labor and Delivery—The effect of Orenitram on labor and delivery in humans is unknown.

No treprostinil treatment related effects on labor and delivery were seen in animal studies.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—Clinical studies of Orenitram did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment—Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure. Titrate slowly in patients with hepatic insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C).

Patients with Renal Impairment—No dose adjustments are required in patients with renal impairment. Orenitram is not removed by dialysis.

OVERDOSAGE

Signs and symptoms of overdose with Orenitram during clinical trials reflect its dose-limiting pharmacologic effects and include severe headache, nausea, vomiting, diarrhea, and hypotension. Treat supportively.

United Therapeutics Corporation, Research Triangle Park, NC 27709
Rx only
January 2016
www.orenitram.com

United Therapeutics CORPORATION

5 measures predict 30-day postop rehospitalization

BY MITCHEL L. ZOLER
Frontline Medical News

PHOENIX – A simple, five-element formula can help identify the patients undergoing heart surgery who face the greatest risk for a hospital readmission within 30 days following discharge from their index hospitalization.

The surgeons who developed this formula hope to use it in an investigational program that will target intensified management resources in postsurgical patients who face the highest readmission risk, to cut rehospitalizations and better improve their clinical status and quality of life.

Fluid overload was the worst offender for triggering rehospitalization following heart surgery.

DR. KILIC

A heart surgery patient typically retains about 5-10 pounds of fluid. Many patients go home prior to diuresis.

DR. CONTE

The analysis that produced this formula also documented that the worst offender for triggering rehospitalizations following heart surgery is fluid overload, the proximate readmission cause for 23% of postsurgical patients, Dr. Arman Kilic said at the annual meeting of the Society of Thoracic Surgeons. The next most common cause was infection, which led to 20% of readmissions, followed by arrhythmias, responsible for 8% of readmissions, said Dr. Kilic, a thoracic surgeon at the University of Pennsylvania in Philadelphia.

Because fluid overload, often in the form of pleural effusion, is such an important driver of rehospitalizations, a more targeted management program would include better titration of diuretic treatment to patients following heart surgery, thoracentesis, and closer monitoring of clinical features that flag fluid overload such as weight.

An investigational program to target rehospitalization risk in heart surgery patients is planned at Johns Hopkins Hospital in Baltimore, where Dr. Kilic worked when he performed this analysis. Surgeons at Johns Hopkins are now in the process of getting funding for this pilot program, said Dr. John V. Conte Jr., professor of surgery and director of mechanical circulatory support at Johns Hopkins and a collaborator with Dr. Kilic on developing the risk formula.

"We'll tailor postoperative follow-up. We'll get high-risk patients back to the clinic sooner, and we'll send nurse practitioners to see them to make sure they're taking their medications and are getting weighed daily," Dr. Conte said in an interview. "When a patient has heart surgery, they typically retain about 5-10 pounds of fluid. Patients with good renal function give up that fluid easily, but others are difficult to diurese. Many patients go home before they have been fully diuresed, and we need to follow these patients and transition them better to out-of-hospital care."

He noted that other situations also come up that unnecessarily drive patients back to the hospital when an alternative and less expensive intervention might be equally effective. For example, some patients return to the hospital out of concern for how their chest wound is healing. Instead of being rehospitalized, such patients could be reassured by having them send a nurse a photo of their wound or by coming to an outpatient clinic.

Developing improved ways to manage recent heart surgery patients following discharge becomes even more critical later this year when, in July, the Centers for Medicare & Medicaid Services adds 30-day readmissions following coronary artery bypass grafting (CABG) to its list of procedures that can generate a penalty to hospitals if they exceed U.S. norms for readmission rates.

The risk model developed by Dr. Kilic, Dr. Conte, and their associates used data collected from 5,360 heart surgery patients treated at Johns Hopkins during 2008-2013. Nearly half the patients underwent isolated CABG, and 20% had isolated valve surgery. Overall, 585 patients (11%) had a hospital readmission within 30 days of their index discharge. One limitation of the analysis was it used data only on readmissions back to Johns Hopkins Hospital.

The researchers used data from three-quarters of the database to derive the risk formula, and from the remaining 25% of the database to validate the formula. A multivariate analysis of demographic and clinical characteristics that significantly linked with an elevated risk for readmissions identified five factors that independently made a significant contribution to readmission risk, assigning each factor points, depending on its relative contribution to readmission risk in the adjusted model: Severe chronic lung disease received 6 points; placement of a ventricular assist device received 5 points, while other types of heart surgery that was not CABG or valve surgery received 4 points (isolated CABG, isolated valve, or combined CABG and valve surgery received 0 points); development of acute renal failure postoperatively but before index discharge received 4 points; an index length of stay beyond 7 days received 4 points; and African American race received 3 points. The maximum number of points a patient could receive was 22.

Patients with a score of 0 had a 6% rate of a 30-day readmission; those with a score of 22 had a 63% readmission rate. The researchers found a 96% correlation when comparing these predicted readmission risk rates based on the derivation-subgroup analysis with the actual readmission rates seen in the validation subgroup of their database. The targeted risk-management program planned by Dr. Conte would primarily focus on high-risk patients.

Dr. Kilic and Dr. Conte said they had no relevant financial disclosures.

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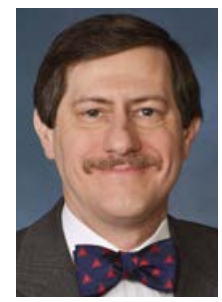
VIEW ON THE NEWS



Dr. Francis J. Podbielski, FCCP, comments: Dr. Kilic's data illustrates common factors resulting in rehospitalization after cardiac surgery. Fastidious fluid management in these patients and others is critical to reduce hospital readmissions. A further point to consider is that many pleural effusions, especially those on the left side, are due to retained hemothorax rather than fluid overload. In those instances, early surgical intervention with video-assisted thoracoscopic surgery, rather than prolonged diuresis, would be optimal.

Cadaveric allograft sternal replacement appears safe

BY DOUG BRUNK
Frontline Medical News

PHOENIX – Cadaveric allograft sternal replacement has proven to be safe, providing optimal stability to the chest wall and protection of surrounding organs, an analysis of 18 cases demonstrated.

"The allograft was biologically well tolerated, allowing a perfect integration into the host," Dr. Giuseppe Marulli said at the annual meeting of the Society of Thoracic Surgeons. "Donor cryopreserved sternochondral allograft may become the ideal way for anterior chest wall reconstruction, particularly for wide resections."

Dr. Marulli, a thoracic surgeon at the University of Padova, Italy, noted that prior experimental studies have demonstrated that cryopreserved bone allografts preserve osteoconduction and osteoinduction capacity (Eur Spine J. 2001 Oct;10:S96-101). "Therefore, they form the basis for new bone tissue formation, allowing for the capillary and perivascular blood supply," he said.

Limitations of current materials used for sternal reconstruction include "excessive rigidity with risk of erosion and insufficient support for large chest wall defects," he said. Perceived advantages of using cadaveric bone allograft include easy incorporation, no risk of rejection, and a low risk of infection. For each procedure used in the current analysis, cadaveric allograft sternums with costal cartilages were harvested with an aseptic method and treated with an antibiotic solution for 72 hours. Next, they were cryopreserved at –80° C and underwent microbiologic testing for at least 1 month to ensure sterility and absence of immunogenic capacity.

Continued on page 45

For reducing the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations

BEFORE ONE EXACERBATION CAN LEAD TO ANOTHER,[1] ADD DALIRESP

INDICATION AND USAGE

DALIRESP® (roflumilast) is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

IMPORTANT SAFETY INFORMATION

Contraindications

DALIRESP® (roflumilast) is contraindicated in patients with moderate to severe liver impairment (Child-Pugh B or C).

Warnings and Precautions

- DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm
- Prescribers should advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur, to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment if such events occur. Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP
  - Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In controlled clinical trials 5.9% of patients treated with DALIRESP reported psychiatric adverse reactions vs 3.3% treated with placebo. The most common psychiatric adverse reactions were insomnia (2.4% vs 1.0%), anxiety (1.4% vs 0.9%), and depression (1.2% vs 0.9%). Three patients treated with DALIRESP experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) compared to one patient (suicidal ideation) treated with placebo
- Patients should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated and treatment discontinuation considered
  - In addition to weight loss being reported as a common adverse reaction (7.5% of patients treated with DALIRESP vs 2.1% placebo), weight was prospectively assessed in two 1-year clinical trials. In these studies that compared DALIRESP to placebo, 20% vs 7% experienced moderate

AstraZeneca

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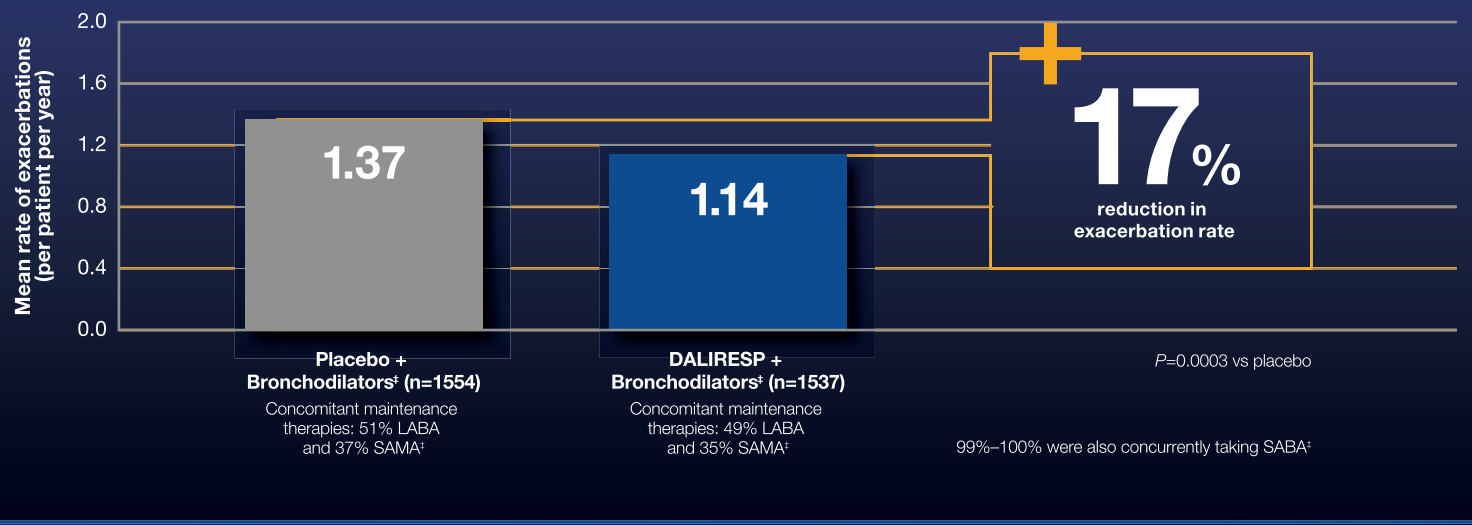
The first and only once-daily tablet to provide enhanced protection against COPD exacerbations*[2]

- **DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm**

In the two 1-year pivotal studies:

Significantly reduced the rate of moderate or severe exacerbations† on top of current bronchodilator therapy‡[3]

REDUCTION IN THE RATE OF EXACERBATIONS VERSUS PLACEBO‡[3]



weight loss (5-10% of body weight) and 7% vs 2% experienced severe weight loss (>10% body weight). During the follow-up period after discontinuing DALIRESP, the majority of patients regained some of the weight they had lost

- Use with strong cytochrome P450 enzyme inducers (eg, rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended, as they decrease the exposure and may reduce the therapeutic effectiveness of DALIRESP

Adverse Reactions

In clinical trials, the most common adverse reactions (≥2% and greater than placebo) were diarrhea (9.5% vs 2.7%), weight loss (7.5% vs 2.1%), nausea (4.7% vs 1.4%), headache (4.4% vs 2.1%), back pain (3.2% vs 2.2%), influenza (2.8% vs 2.7%), insomnia (2.4% vs 1.0%), dizziness (2.1% vs 1.1%), and decreased appetite (2.1% vs 0.4%).

Please see Brief Summary on the following page.

*In the two 1-year pivotal studies, DALIRESP was added to bronchodilators, including long-acting β_2 agonists (LABA), or short-acting muscarinic antagonists (SAMA), and short-acting β_2 agonists (SABA).

†Moderate exacerbations were defined as those requiring treatment with systemic corticosteroids, and severe exacerbations were defined as those resulting in hospitalization or death.

‡Patients were allowed to be on LABA or SAMA at stable doses. SABA was allowed for rescue use. In the pooled analysis, the use of concomitant bronchodilators in the placebo group vs DALIRESP group were: LABA (51% vs 49%), SAMA (37% vs 35%), and SABA (99% vs 100%).

Study design: A pooled analysis of two identical, 1-year, double-blind, placebo-controlled studies of 3091 patients with severe COPD associated with chronic bronchitis and a history of exacerbations compared DALIRESP (n=1537) and placebo (n=1554). Subjects were current or ex-smokers with a smoking history of >20 pack-years, aged >40 with a clinical diagnosis of COPD with chronic cough and sputum production. The study included a 4-week run-in period followed by a 1-year treatment period. Subjects could use SABAs as needed and could continue treatment with LABAs or SAMAs at stable doses. The studies were designed to assess the rate of moderate or severe COPD exacerbations and the change from baseline in pre-bronchodilator FEV_1.

References: 1. Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179:369-374. **2.** DALIRESP Prescribing Information. Wilmington, DE; AstraZeneca Pharmaceuticals LP; November 2015. **3.** Calverley PMA, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; for the M2-124 and M2-125 Study Groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694.

Daliresp®
(roflumilast) tablets
500 mcg

DALIRESP® (roflumilast) tablets

Brief Summary of Prescribing Information.
For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

DOSAGE AND ADMINISTRATION

The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following condition:
Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6) in the full Prescribing Information*].

WARNINGS AND PRECAUTIONS

Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) [*see Adverse Reactions (6.1) in the full Prescribing Information*]. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo. Cases of suicidal ideation and behavior, including completed suicide, have been observed in the post-marketing setting in patients with or without a history of depression.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1) in the full Prescribing Information*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [*see Drugs that Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

ADVERSE REACTIONS

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

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Weight Decrease *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Adverse Reactions in Clinical Studies

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

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP**	**Placebo**
	(**N=**4438)	**(N=**4192)
	n (%)	n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:
Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting
Infections and infestations - rhinitis, sinusitis, urinary tract infection
Musculoskeletal and connective tissue disorders - muscle spasms
Nervous system disorders - tremor
Psychiatric disorders - anxiety, depression

Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of DALIRESP received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to DALIRESP. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to DALIRESP exposure: hypersensitivity reactions (including angioedema, urticaria and rash), gynecomastia.

DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Drugs that Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Drugs that Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses >2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

Labor and Delivery

DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of >2 mg/kg/day).

Nursing Mothers

Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

Pediatric Use

COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

Geriatric Use

Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were >65 years of age and 471 were >75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Renal Impairment

In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

Human Experience

No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

Management of Overdose

In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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Complications after cancer surgery raise death risk

BY NEIL OSTERWEIL
Frontline Medical News

BOSTON – The operation was a success, but the patient died.

It's an old chestnut for sure, but there is a painful kernel of truth in it, say investigators who found that patients who undergo complex cancer surgery and have serious complications are at significantly increased risk for death for at least 6 months after surgery, compared with patients who undergo the same procedure with few or no complications.

"Our work has important implications for quality assessment. I think in cancer surgery in particular we have to get away from the short-term metrics of survival, and we have to think about the implications of complications for long-term survival, even if at a very high-quality hospital we're good at salvaging those patients who do experience those complications," said Dr. Hari Nathan of the University of Michigan, Ann Arbor.

In a retrospective study, results of which were presented at the annual Society of Surgical Oncology Cancer Symposium, Dr. Nathan and colleagues showed that patients who underwent surgery for cancers of the esophagus and lung who had serious complications but survived at least 30 days after surgery had a more than twofold greater risk for death than did patients who had no complications, and patients with serious complications following surgery for cancer of the pancreas had a nearly twofold greater risk.

The effects of serious complications on survival persisted out to at least 180 days after surgery for each of the three procedures.

The findings suggest that just getting the patient through the operation and keeping him or her alive in the ICU is not sufficient cause for celebration by surgeons, Dr. Nathan said.

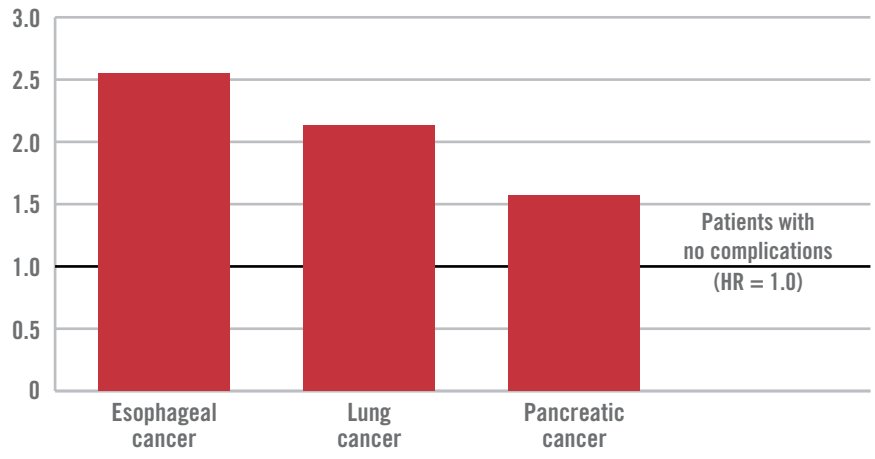
The investigators conducted the study to examine the incidence of complications following cancer surgery in older patients, the relationship between surgical complications and long-term survival, and whether the effects of complications would diminish or "wash out" over time. They reviewed Surveillance, Epidemiology and End Results–Medicare data on patients aged 65 years and older who underwent surgery with curative intent for esophageal cancer, non–small cell lung cancer, or pancreatic adenocarcinoma from 2005 through 2009.

They defined serious complications as "the appearance of a complication associated with a hospital length of stay greater than the 75th percentile for that procedure."

The cohort included 965 patients who underwent esophageal surgery, 12,395 who had lung surgery, and 1,966 who underwent pancreatic resection. The proportion of patients over 80 years who underwent the procedures, respectively, were 12%, 18%, and 19%.

Serious complications occurred in 17% of patients with esophageal cancer, 10% of those with lung cancer, and 12% of those with cancer of the pancreas. The respective 30-day mortality rates were 6%, 3.3%, and 3.9%.

Hazard ratios for death after surgery with serious complications



FRONTLINE MEDICAL NEWS

Note: Based on Surveillance, Epidemiology and End Results-Medicare data for patients who underwent surgery for esophageal cancer (n = 965), non–small cell lung cancer (n = 12,395), and pancreatic adenocarcinoma (n = 1,966).

Source: Dr. Nathan

Looking only at those patients with lung cancer who survived at least 30 days after surgery, the investigators found that median survival among those who had no complications was 79 months, compared with 60 months for those who had mild complications, and 33 months for patients who had serious complications (*P* less than .001)

"And indeed, when we performed adjusted survival analyses looking at all three disease sites, we saw a very consistent story: that those patients who had serious complications had decreased long-term survival for all three malignancies we looked at," Dr. Nathan said.

Specifically, in survival analyses adjusted for sex, age, and procedure code, hazard ratios for patients with serious complications compared with those who had no complications were 2.55 for esophageal cancer patients, 2.13 for lung cancer patients, and 1.57 for pancreatic cancer patients (all comparisons significant as shown by 95% confidence intervals).

The investigators questioned whether the differences in mortality were due to the late effects of perioperative complications.

"In modern ICUs, we can keep virtually anybody alive for 30 days, and there has been a lot interest in longer-term metrics for perioperative mortality, for example, at 30 or 90 days, so we thought maybe that's what we were seeing here," he said. To test this idea, the investigators looked at the effects of complications on patient who survived lung cancer surgery for at least 90 days, and those who lived for at least 180 days after surgery, and they saw that the survival curves were similar to those seen with the 30-day survivors, showing significantly and persistently worse survival for patients with serious complications (*P* less than .001).

For each of the disease states, patients with serious complications were also significantly less likely than were those with no or mild complications to receive adjuvant chemotherapy, even after adjustment for patient age and cancer stage, two significant determinants of the likelihood of receiving chemotherapy.

And even when the effect of chemotherapy for those who did receive it was added into the survival models, patients with serious complications still had significantly worse overall survival, Dr. Nathan noted.

"Serious complications after these three cancer resections are common and they are associated with dramatically inferior long-term survival," he said.

The study was internally funded. Dr. Nathan reported no significant disclosures.

Continued from page 41

Dr. Marulli reported results from 18 patients who underwent the procedure between January 2009 and January 2015, 13 of whom were female. Their median age was 59 years, their median tumor diameter was 4.75 cm, most (88%) had undergone preoperative needle biopsy, and 50% had undergone induction therapy. The main indication for sternectomy was a single-site sternal metastasis (nine patients), primary chondrosarcoma (four cases), sternal dehiscence after cardiac surgery (two cases), malignant fibrous tumor (one case), radioinduced soft-tissue sarcoma (one case), and a thymic carcinoma invading the sternum (one case).

The allograft was biologically well tolerated, allowing a perfect integration into the host.

DR. MARULLI

All patients were extubated in the OR, and one patient died in the hospital from a pulmonary embolism. Two patients (11%) developed postoperative complications: one case of *Candida* urinary infection and one case of bleeding at the site of the muscle flap. The median postoperative length of stay was 11 days.

To date, no infections or rejections of the grafts have occurred, Dr. Marulli said. After a median of 36 months, 13 patients are alive and 4 are dead (3 from a metastatic recurrence and 1 from an unrelated cause). One patient required removal of a clavicular screw for dislocation 4 months after the operation.

"The outcomes [of these procedures] appear to be excellent," said Dr. Francis J. Podbielski, FCCP.

Dr. Marulli reported having no financial disclosures.

dbrunk@frontlinemedcom.com

Top 5 EHR companies agree to halt data blocking

BY CHERYL CLARK
Frontline Medical News

LAS VEGAS – Health care data interoperability should get a huge boost under a public-private effort announced Feb. 29 by U.S. Department of Health and Human Services Secretary Sylvia Burwell.

The nation's top five health care systems and companies, which provide the electronic health record systems that cover more than 90% of U.S. hospital patients, have agreed to principles designed to improve patient access to health data and eliminate the practice of data blocking.

They also have agreed to adopt federally recognized, national interoperability standards, Ms. Burwell announced at the annual meeting of the Healthcare Information and Management Systems Society.

"Technology is not just one leg of our strategy to build a better health care system for our nation – it supports the entire effort," Ms. Burwell said. "We are working to unlock health care data and information so that providers are better informed and patients and families can access their health care information, making them empowered, active participants in their own care."

In a show of support, medical specialty societies including the American Academy of Family Physicians, the American College of Physicians, the American Society of Clinical Oncology, and the American Medical Association also signed on to the commitment.

"We have made tremendous progress to bring health care into the 21st century," Ms. Burwell said. "In 6 short years, we have tripled the adoption of electronic health records. Today, three-quarters of physicians are using them. And nearly every hospital uses EHRs, meaning that there is now a digital care footprint for almost everyone in this country."

We are working to unlock health care data and information so that providers are better informed.

MS. BURWELL

To unlock all those data and make them useful to health care providers and patients, the health IT companies and health care systems have agreed to the following steps:

- Implement application programming interface (API) technology so that smartphone and tablet apps can be created, facilitating patient use and transfer of their health care data.
- Work so providers can share patient health care data with patients and other providers whenever permitted by law, while not blocking such sharing either intentionally or unintentionally.
- Use the federally recognized Fast Healthcare Interoperability Resources (FHIR) data standard.

This commitment is a "major step forward" to help patients "not just in one episode, but over the long term," explained Dr. Karen DeSalvo, National Coordinator for Health Information Technology. The agreement means the health care system is "on the threshold of a truly historic opportunity to transform quality of care," she added.

Federal officials have a timeline for progress toward these goals by 2018, Dr. DeSalvo noted. But "the private sector wants to pull that forward and be leaders with us," she said. "So, our expectation is that the calls and the commitments and the associated actions that these developers have declared will be seeing some changes by the fall."

To highlight health information technology's promise, Ms. Burwell shared a story about electronic health records' use to find children affected by lead pollution in the water supplies of Flint, Mich.

Alerted to the problem by a friend, pediatrician Mona Hanna-Attisha of Hurley Medical Center in Flint tried to determine whether pipe corrosion might leach dangerous levels of lead into the water supply, Ms. Burwell said.

"She knew the danger lead posed and began what she called a 'crusade' to find out if it was affecting children," Ms. Burwell explained. Dr. Hanna-Attisha mined Hurley's medical records to "compare blood test results from more than 700 children in the area and map home addresses for geographic variations.

"She quickly discovered that the percentage of children in Flint with lead poisoning had doubled,

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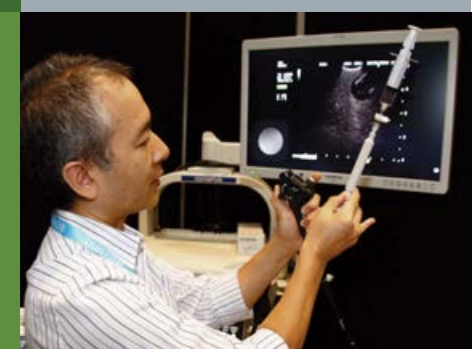

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and even tripled, in some neighborhoods," Burwell said.

If those results had still been on paper, "it would have taken forever to get these results," she said.

"Dr. Hanna-Attisha's story shows us the power of putting health care data to work," Ms. Burwell noted. "It ... helps us put patients in the center of their care."

VIEW ON THE NEWS

Dr. Mike Nelson, FCCP, comments: If this agreement leads to substantive changes in the current EHR quagmire it will indeed be a huge benefit for physicians and patients alike. There is little more frustrating to both the patient and the physician than having to evaluate an individual whose records are "locked" in another hospital's system. The adoption of federal standards should result in a significant improvement in the current situation although, as stated in the article, implementation may be slow and difficult. I would offer Ms. Burwell the following suggestion; invent a process called "Meaningful Implementation" and tax EHR vendors 2-8% for each year they do not comply.

HRSA redefines 'investigation'

BY ALICIA GALLEGOS
Frontline Medical News

AUSTIN, TEX. – Physicians could face more reportable actions to the National Practitioner Data Bank (NPDB) under changes to the data bank's guidebook.

In its last update of the guidebook, the Health Resources and Services Administration (HRSA) expanded its definition of "investigation" and now interprets the term "expansively" and will not be limited by how hospital bylaws define an investigation.

Data bank officials will review a health care entity's bylaws and other documents for assistance in determining whether an investigation has started or is ongoing, but they retain "the ultimate authority to determine whether an investigation exists," according to the guidebook.

The change is significant because it means more reviews by health care entities could be considered investigations by the data bank, regardless of how hospitals regard the assessment, Michael A. Cassidy said at the meeting, which was held by the American Health Lawyers Association.

Investigations alone are not reportable to the data bank, but actions taken by doctors during investigations are. This includes:

- Resignation of clinical privileges.
- Failure to renew clinical privileges.
- Lapse of license.
- Leave of absence.
- Relinquishment of panel membership.

The guidebook notes that a routine, formal peer review process under which a health care entity evaluates, against defined measures, privilege-specific competence of all practitioners is not considered an investigation by the NPDB. However, a formal, "targeted process used when issues related to a specific practitioner's professional competence or conduct are identified" is considered an investigation for purposes of reporting to the NPDB.

The catch for doctors is that their awareness of an investigation is immaterial, said Mr. Cassidy, a Pittsburgh-based health law attorney. In the past, a doctor's awareness of an investigation was a prerequisite for filing a report with the data bank.

The HRSA's stance is that "physicians' awareness of the investigation doesn't have any impact on whether it's an investigation or not," Mr. Cassidy said in an interview. "From a physician standpoint, they want to be aware all the time whether an investigation has started. If they don't find out an investigation has started until after they get a decision, it's too late to forestall any of the reporting consequences."

In addition, the NPDB considers an investigation ongoing until the health care entity takes a final action or formally closes the investigation. Written notice to the doctor would likely be the best evidence of formal closure, Mr. Cassidy says.

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Lights, camera, action! CHEST 2016 visits Los Angeles

We're gearing up to visit the entertainment capital of the world on October 22 - 26 for CHEST 2016. We will dazzle Los Angeles and the chest medicine community with current pulmonary, critical care, and sleep medicine topics presented by world-renowned faculty in a variety of innovative instruction formats. You won't want to miss our cutting-edge education; and, in your free time, we want to make sure you take in all that Los Angeles has to offer. Follow our suggestions below, and we'll make sure you've seen the most famous hot spots in LA.

Hollywood

When you think of Los Angeles, Hollywood is sure to be top of mind. Hollywood is about a 25-minute drive from the Convention Center, so make sure you have time for a longer excursion. You'll enjoy the recognizable Hollywood sign, built in 1923, and the Hollywood Walk of Fame. You can also check out the Dolby Theater, home to the Academy Awards until at least 2033, or Runyon Canyon, a famous park known for great views of the city and celebrity sightings.

Beaches

If Hollywood doesn't allure you, maybe you'd rather take it easy at one of Los Angeles's famous beaches. If you like to people watch, Venice Beach will keep you interested with body builders, jugglers, palm readers, folk artists, and other personalities. If you're interested in surfing, Malibu Surfrider Beach is where amateurs and experienced surfers alike find great waves. Santa Monica Beach is popular for its volleyball, bike riding, and sunbathing. Or check out Long Beach, home to the Queen Mary, a floating hotel aboard an iconic 1936 ocean liner. With 75 miles of coast, you're sure to find the beach that you're looking for.

Shopping

Make sure to explore the LA Fashion District in downtown LA, where you'll find many top shopping centers to choose from. If you're looking for luxury, Rodeo Drive in Beverly Hills offers extravagant shopping and dining experiences. Or, if you're intrigued by bargain hunting, there are also plenty of opportunities for outlet shopping in Camarillo, the Citadel, Desert Hills, and Ontario Mills.

Television Show Taping

Maybe you've always dreamed of being part of a live studio audience. Choose from a wide array of shows filmed in Los Angeles, and lucky you, October is in the heart of peak production season. If you want to attend a show taping, order tickets in advance. Check out a vendor, such as Audiences Unlimited or Hollywood Tickets, both of which feature sitcoms and talk shows. You can also look at a specific show's website to find tickets. Attending a TV show taping can be an exciting and unique LA experience, and, best of all, it's free!

Los Angeles will keep you entertained with its glamour and glitz. Learn more about tourism opportunities at discoverlosangeles.com, and find out more about CHEST 2016 at chestmeeting.chestnet.org.

CHEST Foundation Grants: How will you champion lung health?

The CHEST Foundation expanded its grant offerings in 2016 with the addition of two new research grants that will broaden the program's reach and scope. As of February 1, the foundation began accepting applications for research grants, community service projects, and distinguished scholar research projects. These grants have a powerful impact on our grantees' ability to champion lung health, and they also assist young investigators like Dr. Kerri Johannson in gaining research and project management skills, while assisting in advancing their careers.

"Being awarded a grant is validation that somebody else believes in your idea and that your project could be fruitful and contribute meaningfully to the field," stated Johannson. "It actually begets more opportunities. I am forever grateful to the CHEST Foundation for providing me with this opportunity." The CHEST Foundation's Clinical Research Grant in Pulmonary Fibrosis, along with Genentech, funded her 2013 project, Ambient Air Pollution Exposure and Clinical Outcomes in Idiopathic Pulmonary Fibrosis. Dr. Johannson's research focuses on analyzing air pollution exposures and short-term variability in lung function for patients with idiopathic pulmonary fibrosis (IPF).

Her patients were given home breathing machines to monitor how their lung function fluctuated over shorter periods of time. "I was interested in looking at whether or not and how that correlated with their air quality in the regional area." She said about her project, "No one has ever looked at it before. It's usually a long-term study, such as every 3 months or changes over a year in clinical trials, but it turns out there is actually a large portion of patients with a lot of short-term variability that has an impact for clinical trial outcomes and measures."

The deadline for applications is quickly approaching. CHEST Foundation grants help make your research and community service projects possible. Please take advantage of our substantive grant program, and remember that the submissions will be accepted until April 30. How will you help champion lung health? Apply for a CHEST Foundation grant today by going to chestnet.org/grants.

In Memoriam

Dr. Robert O. Crapo, FCCP, died on December 26, 2015. He was a Professor of Medicine at the University of Utah and the Director of the Pulmonary Function Laboratory at LDS Hospital, a laboratory that was internationally regarded for many contributions to understanding pulmonary function and pulmonary function testing. At this teaching laboratory where countless fellows, residents, and students learned the principles of pulmonary function testing, basic respiratory physiology, and how lung function tests could help them diagnose and treat lung disease, Dr. Crapo was a master teacher. Dr. Crapo received the 2006 Distinguished Scientist Honor Lecture award from the American College of Chest Physicians. We extend our condolences to the Crapo family.

This Month in *CHEST*: Editor's Picks

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

Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. *By Dr. G. Singh et al.*

Brain Imaging for Staging of Patients With Clinical Stage IA Non-small Cell Lung Cancer in the National Lung Screening Trial: Adherence With Recommendations From the Choosing Wisely Campaign. *By Dr. A. A. Balekian et al.*

Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies. *By Dr. K. Dahal et al.*

CONTEMPORARY REVIEWS IN CRITICAL CARE

Crises in Sickle Cell Disease. *By Dr. E. M. Novelli and Dr. M. T. Gladwin.*

TOPICS IN PRACTICE MANAGEMENT

Developing an Interventional Pulmonary Service in a Community-Based Private Practice: A Case Study. *By Ms. K. French et al.*

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Lauren Morgan
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FRONTLINE MEDICAL COMMUNICATIONS

NETWORKS: EBUS coding, asbestos, end-of-life care, respiratory therapy education, drowsy driving

Interventional Chest/ Diagnostic Procedures

New EBUS coding, CMS billing delays

On January 1, 2016, AMA CPT® created three new codes to describe endobronchial ultrasound (EBUS) procedures. These new codes were designed to better describe the actual service provided and incorporate the transbronchial needle aspiration (TBNA) into that service. CPT **31652** should be reported with aspiration of two or fewer mediastinal or hilar lymph node stations or structures, and CPT **31653** should be reported with aspiration of three or more mediastinal or hilar lymph node stations lymph node stations or structures. The older code for EBUS alone (**31620**) is now no longer available. The use of the radial probe EBUS now uses the ZZZ or add-on CPT code **31654** similar to the old CPT **31620** EBUS code. As an add-on, CPT **31654** must be used with another bronchoscopy code such as transbronchial biopsy (CPT **31628**) or transbronchial needle aspiration when used in the periphery (**31629**). It is not appropriate to use CPT **31629** (TBNA) concurrently with the **31652** or **31653** CPT codes.


DR. GILDEA

When these new codes were sent through the process of the National Correct Coding Initiative (NCCI), an error occurred such that some appropriate code pairs were deemed inappropriate by the software, resulting in claims being rejected, denied, or underpaid. ATS and CHEST notified the NCCI contractor and CMS, who agreed that there was, in fact, an error and it would be corrected as of April 1, 2016, since corrections get updated quarterly. It was recommended that all EBUS claims be held until April 1, 2016, or that members should be prepared to resubmit or ask for adjudication of improperly paid claims based on the updated NCCI edits.

Code descriptors below:

- **31652** with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), one or two mediastinal and/or hilar lymph node stations or structures
- **31653** with endobronchial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]), 3 or more mediastinal and/or hilar lymph node stations or structures
- **31654** with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s) (List separately in addition to code for primary procedure[s])

Dr. Thomas Gildea, FCCP
Steering Committee Member

Occupational and Environmental Health

Asbestos in Libby, MT

The Occupational and Environmental Steering Committee has interest in occupational and environmental exposures and their impact on economically disadvantaged populations. Exposure to vermiculite caused a public health emergency in Libby, MT.

There were 5.8 million tons of vermiculite ore mined and milled 6 miles from Libby from 1923 until 1990. Ore was contaminated with (26% by weight) Libby amphiboles (LA) asbestos.

LA contained 6% tremolite asbestos, 84% winchite, and 11% richterite. Daily dust release from the mill of 5,000 to 10,000 pounds contam-

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UNIVERSITY OF LOUISVILLE

Chief, Division of Pulmonary, Critical Care and Sleep Medicine

The University of Louisville invites applications for Chief of the Division, which includes 15 faculty and 10 fellows that staff specialized programs in cystic fibrosis, interstitial lung disease, pulmonary hypertension, interventional pulmonology, lung transplantation, sleep medicine, and critical care. The clinical enterprise spans the University Hospital, VA Hospital, and Jewish Hospital in downtown Louisville. Research includes clinical trials as well as basic research in oxidant stress, neural control, and lung injury and repair, rejection after transplantation, and cancer. The successful candidate will be at the Associate or Professor level, will hold an endowed chair, will have support to recruit additional faculty and will provide leadership for the Pulmonary/CCM, Interventional, and Sleep Fellowship Training Programs, research, and clinical missions. Candidates must be board certified in Internal Medicine and Pulmonary and BC/BE in Critical Care. The tenured, academic appointment and compensation will be commensurate with the successful candidate's level of development.

Interested applicants should send CV to Jesse Roman, M.D.
Chairman, Department of Medicine, University of Louisville
530 S. Jackson Street, Louisville, KY 40292
j.roman@louisville.edu

The University of Louisville is a non-discriminatory, affirmative action employer and encourages women and minorities to apply.

NORTH CAROLINA

Winston Salem —– Salem Chest Specialists (**www.salemchest.com**) is an 11 physician private practice, single specialty group looking for a BC/BE Pulmonary/Critical Care Physician with opportunities in Sleep Medicine.

Affiliated with Forsyth Medical Center, a 900 bed community based, tertiary care and referral center, we are looking to expand to 12 MD's to accommodate 24 hour staffing of the 30 bed closed ICU.

Founded in 1983, SCS maintains a busy outpatient practice with full interventional pulmonology program, a clinical research program, and a seven bed accredited sleep center. Located within 40 minutes of Appalachian Mountains, 3.5 hours to the NC Coast, and 45 minutes to Charlotte, Winston Salem provides an ideal environment for balancing work and family life.

Highly competitive salary, benefits, partnership opportunity, and relocation assistance await qualified candidates.

Serious applicants only.
No J-1 Visa.

Please send CV to our office manager, Tammy Ferrell, 336-760-6918 fax, or email: **tferrell@salemchest.com**

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inated a forest and a dam construction site. Slag was applied on athletic fields in the town; 60,000 to 80,000 persons were exposed, many at a young age.

Lincoln County, MT, has the highest asbestosis death rate in the United States, three times higher than Somerset County, NJ (Johns Manville).

When heated to 900 degrees Fahrenheit, the ore "exfoliates" and is used as insulation. Ore was shipped to over 200 expansion plants throughout North America. Asbestosis has been described as occurring in workers and nearby residents of expansion plants. EPA estimated 13 million people lived near expansion plants and that 106 million people had been exposed to the final product (7% LA).

The Center for Asbestos Related Diseases in Libby is concerned for a new phenotype of asbestos-related pleural disease, constituting very thin circumferential diffuse pleural thickening involving only the parietal pleura; progressive loss of pulmonary function, and affecting significantly more than 10% of those exposed. They have expressed concern (personal communication) as to whether particular properties of Libby amphiboles (including nonasbestos winchite and richterite) are leading to this phenotype. Case series are in preparation.

The public health emergency in Libby, MT, and disease in those exposed as end users will be presented at CHEST 2016.

References

Rohs AM, Lockey JE, Dunning KK, et al. *Am J Respir Crit Care Med.* 2008;177(6):630-637.

Black, et al. Rapid progression of pleural disease due to exposure to Libby amphibole. *Am J Ind Med.* 2014;57(11):1197-1206.

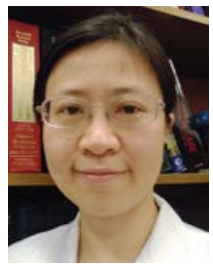
Dr. Richard Evans, FCCP
Chair

Palliative, End-of-Life Care

Care when the "end" is not always clear

Patients with COPD experience disabling symptoms and emotional distress in the last year of life, rating quality of life (QoL) poor or worse than those with end-stage lung cancer (Gore et al. *Thorax.* 2000;55[12]:1000). Only 20% have advance directives (Spathis et al. *Int J Chron Obstruct Pulmon Dis.* 2008;3[1]:11). Patients with COPD utilize more resource-intense care (hospital/ICU stay and mechanical ventilation) in the last 90 days of life compared with patients with cancer or dementia (Teno et al. *JAMA.* 2013;309[5]:470).

Differences in end-of-life (EoL) experiences between patients with COPD and other patients were attributed to COPD's disease trajectory.



DR. YOUNG

Patients with lung cancer or neuromuscular disorders can expect a period of functional stability, followed by sharp decline. COPD patients have progressive decline punctuated by acute exacerbations, leading to outcomes ranging from recovery to baseline to unexpected death. The unpredictable rate of decline and nature of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) result in overoptimistic prognostication and delay in initiating EoL care.

The 2011 Global Initiative on Chronic Obstructive Lung Disease (GOLD) marks a shift in the treatment paradigm: patients are risk stratified based on symptom burden, exacerbations, and airflow obstruction. Those with GOLD Group D have increased mortality risk and should be engaged in EoL discussions. For patients experiencing AECOPDs, recent research identifies mortality risk factors: dyspnea at rest, radiographic consolidations, acidemia, atrial fibrillation (Echevarria et al. *Thorax.* 2016;71[2]:133), and eosinophilia (Bafadhel et al. *Am J Respir Crit Care Med.* 2011;184[6]:662).

We cannot predict which AECOPD will be the final one for our patients; we can safeguard autonomy and QoL by educating patients about the nature of the disease and discussing advanced care planning when there are clear signals that the "end" is near.

Dr. Alisha Young
Steering Committee Physician-in-Training

Respiratory Care

May you live in interesting times!

This expression has never been a truer statement for our respiratory therapist (RT) colleagues.

On January 6, 2016, the American Association of Respiratory Care (AARC) released a statement on RT education, stating, "Training and education for entry-to-practice as a respiratory therapist should be provided within programs awarding a bachelor's or master's degree in respiratory care ... all newly accredited respiratory care educational programs must award, as a minimum, the bachelor's degree in respiratory care." The Commission on Accreditation for Respiratory Care (CoARC) followed 3 weeks later with changes that would stop credentialing new associate degree training programs after January 1, 2018. Both actions move RT closer to the vision articulated by the AARC in its 2015 and Beyond Project.

These steps recognize the complexity of health care and the need for advanced technical and interpersonal skills as health care becomes more team based. RTs with advanced skills are increasingly needed for education, management, and advanced clinical practice. Current examples include COPD patient navigators and readmission reduction programs in which RTs are uniquely qualified to provide value to patients. State licensing boards are also recognizing the changing landscape. California and Ohio both now require the registered respiratory therapist (RRT) certificate for licensure and several other states are considering similar changes.

What does this mean for us? In the short term, most (currently 85%) new RTs will continue to graduate from associate degree programs. Additional education (degree completion, baccalaureate, and masters/doctoral training), however, will become increasingly important for RTs as they assume more diverse and important roles in our health-care system.

Dr. Kevin M. O'Neil, FCCP
Chair

Sleep Medicine

Sleep NetWork update

The Sleep NetWork had several late-breaking sessions at CHEST 2015 in Montréal, including a symposium reviewing the SERVE-HF Study results.

The study revealed an increased risk of cardiovascular death in symptomatic heart failure patients (NYHA II-IV, LVEF less than or equal to 45%) with central apnea (AHI greater than 15 with greater than 50% of central events and CAI greater than or equal to 10) when treated with adaptive servoventilator (ASV) as compared with no ASV use (Cowie et al. *N Engl J Med.* 2015;373[12]:1095).

The discussion was centered on the clinical applicability of these results given several methodological and study design concerns, which affect the generalizability of the findings. Caution was recommended when considering ASV treatment for heart failure patients to ensure they don't fall into this high-risk category. Future research will help delineate the best treatment approaches for these patients.

More recently, the Sleep NetWork endorsed a consensus statement by the National Sleep Foundation (NSF) on drowsy driving.

DR. DAS

DR. KRIEGER

Driving while sleep-deprived yields a performance similar to driving while under the influence of alcohol (Dawson et al. *Nature.* 1997;388[6639]:235).

While many technologies have been developed to decrease collisions in drowsy drivers, the optimal way to improve safety is to decrease the incidence of drowsy driving.

Dr. Barbara Phillips, MSPH, FCCP, was appointed as the CHEST representative to the NSF Drowsy Driving Consensus Work Group.

They concluded that drivers who have slept for 2 hours or less in the preceding 24 hours are not fit to operate a motor vehicle. This statement will have implications for commercial drivers, shift workers, and even clinicians.

Dr. Aneesa Das, FCCP
Steering Committee Chair
Dr. Ana Krieger, FCCP
Steering Committee Member

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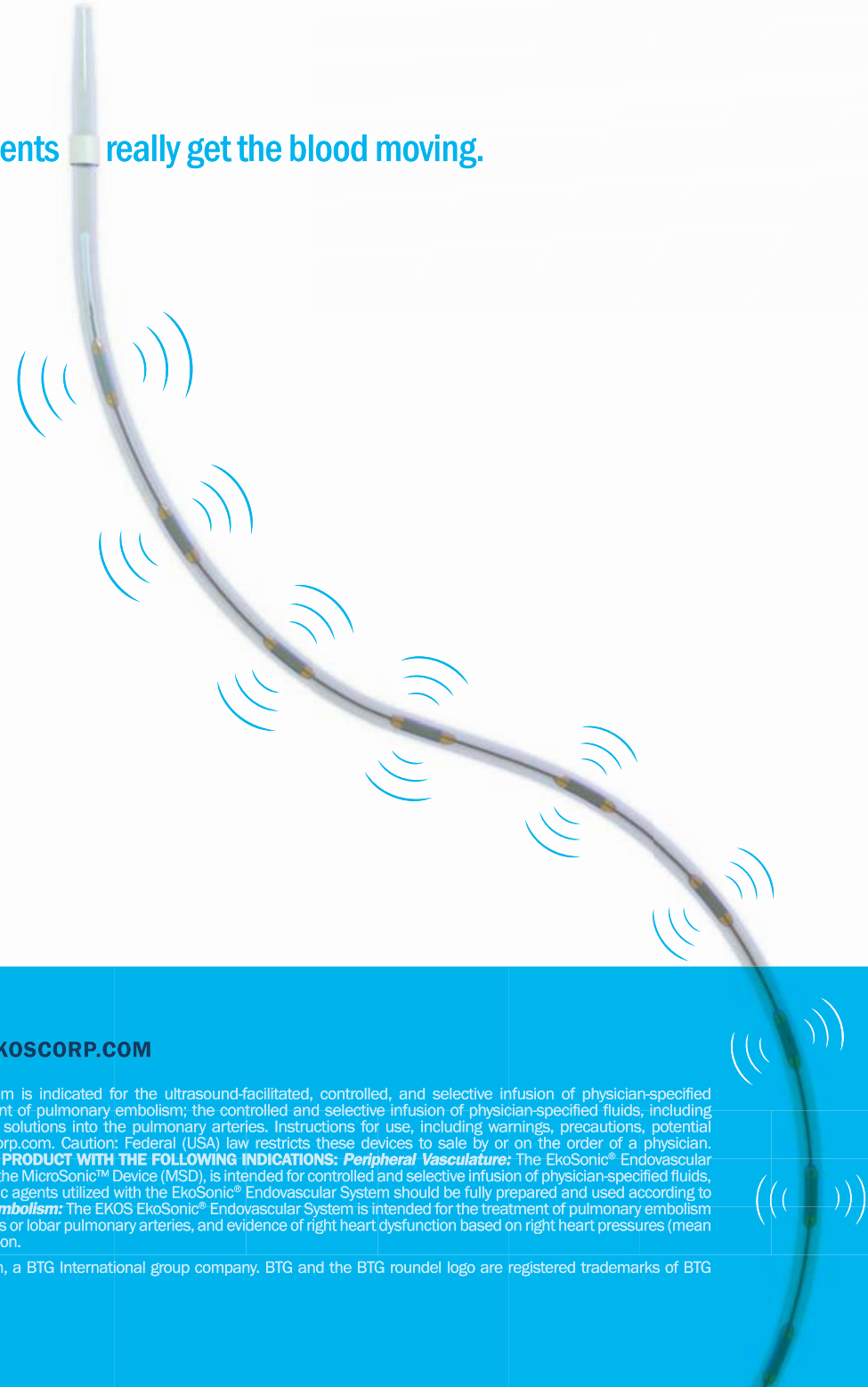

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