

FDA: Get Ready For Phasing Out Of CFC Inhalers

BY JEFF EVANS
Senior Writer

In a public health advisory, the Food and Drug Administration urged health care professionals and their patients and caregivers to switch to hydrofluoroalkane-propelled albuterol inhalers before chlorofluorocarbon-propelled inhalers are taken off the market Jan. 1, 2009.

Chlorofluorocarbon (CFC)-propelled albuterol inhalers will not be produced or sold in the United States in 2009 and beyond in order to meet mandates authorized by the Clean Air Act and an international environmental treaty, the Montreal Protocol on Substances That Deplete the Ozone Layer. CFCs contribute to the depletion of the ozone layer.

Three hydrofluoroalkane (HFA)-propelled albuterol inhalers have been approved by the FDA: Proair HFA Inhalation Aerosol, Proventil HFA Inhalation Aerosol, and Ventolin HFA Inhalation Aerosol. An inhaler containing levalbuterol (similar to albuterol) is available as Xopenex HFA Inhalation Aerosol. HFA-propelled albuterol inhalers are not currently available in generic forms.

"Manufacturers of the HFA versions have created financial assistance programs and eased income restrictions for low-income patients. Physician, pharmacy, and manufacturer's Web sites are also offering coupons for those who face a higher copay for these products," said Deborah Henderson, senior adviser in the Office of Executive Programs at the FDA's Center for Drug Evaluation and Research.

The spray from HFA-propelled inhalers may taste and feel different than CFC-propelled inhalers. The properties of HFA and the weaker force of its spray from the inhalers make it "important to clean and prime the inhalers in order for the right dose of medicine to be delivered. Patients should be reinforced with the knowledge that they need to follow the directions very carefully," Ms. Henderson said in a press teleconference.

The changes do not affect the medication's safety or effectiveness, she noted.

In the beginning of 2008, HFA-propelled albuterol inhalers composed only 5%-10% of albuterol inhaler sales in the market—even though the FDA in 2005 had finalized the end date for the sale of CFC-propelled albuterol inhalers. HFA-propelled albuterol inhalers now account for about 65% of the market, according to Dr. Badrul Chowdhury, director of the Division of Pulmonary and Allergy Products at the FDA's Center for Drug Evaluation and Research.

About 52 million albuterol metered-dose inhalers are prescribed in the United States each year, making them among the top 10 prescribed medications in the country, Dr. Chowdhury said during the teleconference.

Over the years, many manufacturers have stopped producing CFC-propelled albuterol inhalers. Currently, only one company, Armstrong Pharmaceuticals Inc., manufactures generic CFC-propelled albuterol inhalers, he said. ■

Resistance Thwarts Asthma Control

BY NANCY WALSH
New York Bureau

TORONTO — Steroid resistance is increasingly being recognized as a factor contributing to uncontrolled asthma and progression of lung disease, according to a pediatric allergy/immunology expert.

Resistance to inhaled corticosteroids is more common than was previously recognized, and can be found in 25%-35% of patients with asthma.

"In general, steroids are extremely effective in asthma, and really are the most effective anti-inflammatory drugs we have; but in any study of inhaled steroids in asthma, there is remarkable variability in response," said Dr. Donald Y.M. Leung, head of pediatric allergy and immunology at the National Jewish Medical and Research Center, Denver.

Multiple factors can contribute to steroid resistance, including genetics and ethnicity, with blacks being affected more com-

monly than whites, he said at an international conference of the American Thoracic Society. Allergen exposure, smoking, and obesity also have been implicated.

Steroid sensitivity is defined as a greater-than-20% improvement in FEV₁ (forced expiratory volume in 1 second) from baseline after a week of treatment with oral prednisone in doses of 20 mg twice a day, whereas steroid resistance is a less-than-15% improvement, Dr. Leung said.

Investigations of patients who are



In the treatment of painful Diabetic Peripheral Neuropathy (DPN) and Postherpetic Neuralgia (PHN),

W e l c o m e

Selected safety information: LYRICA is indicated for the management of Fibromyalgia, neuropathic pain associated with Diabetic Peripheral Neuropathy, Postherpetic Neuralgia, and as adjunctive therapy for adults with Partial Onset Seizures.

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its other components.

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. LYRICA should be discontinued immediately in patients with these symptoms.

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. LYRICA should be discontinued immediately in patients with these symptoms.

In controlled studies, a higher proportion of patients treated with LYRICA reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions.

Patients with a history of drug or alcohol abuse may have a higher chance of misuse or abuse of LYRICA.

steroid resistant found that they have persistent airway activation, with elevations in interleukin-2, -4, -5, -8, and -13, as well as tumor necrosis factor, despite the use of prednisone. Those cytokines target different cell types, with IL-2 and IL-4 being capable of inducing steroid resistance in T cells, IL-8 inducing resistance in neutrophils, and IL-13 inducing resistance in monocytes and macrophages, he said.

Recent studies have shown that steroid-resistant patients also have increased levels of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in their bronchoalveolar lavage samples. Those molecules control collagen

deposition, and a correct ratio of them is needed to prevent airway remodeling. Patients who are steroid resistant have an imbalance between MMPs and TIMPs, and more ongoing protease activity. Steroids' inability to enhance TIMP-1 production contributes to the abnormal MMP/TIMP ratio in steroid resistant patients. The result of those abnormalities is modification of airway wall matrix deposition, remodeling, and irreversible lung disease (J. Allergy Clin. Immunol. 2007;120:1065-72).

"We have also investigated the mechanisms by which resistance develops [and] have found that a key element in corticosteroid action is the ability to induce nuclear

translocation of the glucocorticoid receptor from the cytoplasm into the nucleus," Dr. Leung said. The anti-inflammatory effects of those drugs are mediated through the α (rather than the β) isoform of the glucocorticoid receptor, he explained.

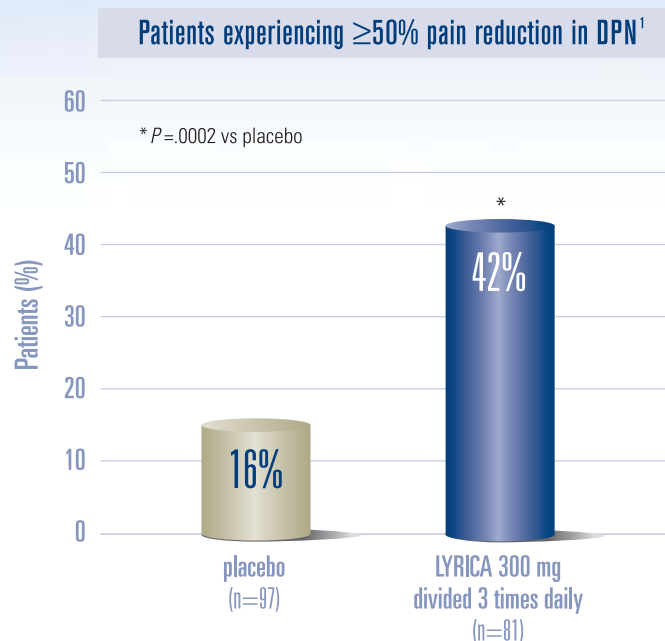
Bronchoalveolar lavage samples from patients who have steroid-resistant asthma have been shown to have reduced α -receptor translocation in response to the drugs, as well as overexpression of its endogenous inhibitor, the β receptor. "The inflammatory milieu in the airways of these patients is driving up the expression of the β receptor." Microbial superantigens also can induce T-cell resistance to steroids,

suggesting a possible role for infection in the development of resistance, he said.

That superantigen-induced resistance can occur via a specific T-cell receptor signaling pathway involving the mitogen-activated protein kinase and the extracellular signal-regulated kinase, leading to phosphorylation of the α receptor of the glucocorticoid receptor and inhibition of nuclear translocation (J. Allergy Clin. Immunol. 2004; 114:1059-69). Those studies suggest that the glucocorticoid receptor itself might be a potential therapeutic target in resistant asthma, he noted. Dr. Leung said he has no financial relationship with a commercial entity involved in this work. ■

t o c a l m

LYRICA provides powerful pain relief in DPN and PHN



- LYRICA also demonstrated significant pain reduction in 3 pivotal PHN studies³

Adapted from Lesser et al. *Neurology*. 2004.²

Results from a 5-week, double-blind, placebo-controlled, multicenter study of 337 patients with moderate-to-severe pain of DPN. Randomized patients received LYRICA 25 mg, 100 mg, 200 mg, or placebo, all given 3 times daily. The primary efficacy parameter was end point least-squares mean pain score on a numeric scale ranging from 0 (no pain) to 10 (worst possible pain) taken from patient diaries. For this responder rate analysis, patients who did not complete the study were assigned a 0% improvement, known as baseline observation carried forward (BOCF) analysis.

Selected safety information: The most common adverse reactions occurring during Fibromyalgia and/or other controlled clinical trials for patients taking LYRICA vs those taking a placebo were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, constipation, euphoric mood, balance disorder, increased appetite, and thinking abnormal (primarily difficulty with concentration/attention).

References: 1. Data on file. Pfizer Inc, New York, NY. 2. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*. 2004;63:2104-2110. 3. Prescribing Information for LYRICA® (pregabalin) capsules ©. Pfizer Inc, New York, NY.

www.pfizerpro.com/lyrica

Please see adjacent brief summary of prescribing information.

LYRICA
PREGABALIN
capsules

Calming the storm