PRIMUS PHARMACEUTICALS

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Re: Limbrel® Safety Update

Dear Limbrel Prescriber,

We are providing this detailed informational letter concerning the safety of Limbrel as an update to a similar notification we issued in 2010. Our original letter was based on 7 years of post-marketing experience in approximately 230,000 patients prescribed Limbrel. This new update is based on additional experience over a cumulative period of nearly 14 years in an estimated 450,000 patients, accounting for more than 1,700,000 prescription sales and sample units. This update is precipitated by the FDA's recent posting of a safety alert for Limbrel. There are two primary safety concerns: hypersensitivity pneumonitis and elevated liver function tests (LFTs).

Hypersensitivity pneumonitis is also called 'extrinsic allergic alveolitis' (and other synonyms) and common names such as farmer's lung, pigeon breeder's disease and many others. This is an allergic pneumonitis due generally to exposure to inhaled antigens, but is also reported in association with a variety of ingested drugs and chemicals. More than 200 antigens have been described, many of which are of fungal or bacterial origin. There are acute, subacute and chronic forms associated with occupational exposures, though Limbrel has only been associated with acute disease. This usually presents with dyspnea and dry cough, often fever and chills, associated with hypoxemia and diffuse patchy pulmonary infiltrates which may be faint and difficult to see on chest x-ray. Blood counts are generally normal but peripheral eosinophilia suggests an alternate diagnosis. Serum IgG precipitating antibodies to defined antigen are characteristic but often difficult to detect if the antigen is unknown. Treatment involves discontinuance of Limbrel and, if necessary, a short course of corticosteroids, often initially given i.v. if the patient is hospitalized. Many cases are initially misdiagnosed as viral or bacterial pneumonia and treated with antibiotics. Patients may improve (unrelated to the antibiotic treatment) but relapse once they are discharged and resume Limbrel. Unfortunately, this appears to be a random event with no predictive or predisposing factors such as history of lung disease, allergy or atopy, although we are continuing to further investigate this issue. This is a relatively rare event with Limbrel. From 2004 to date, Primus has received 31 confirmed and 18 unconfirmed reports of hypersensitivity pneumonitis, although the FDA may have received additional reports not known to Primus which we will analyze as soon as they are released by the FDA. Of the cases reported to Primus, all patients have recovered without residua within 2-4 weeks, though fatigue may last a few weeks longer.

Drug induced liver injury (DILI) is a complication of many medications. While some are due to direct chemical toxicity, most, including those due to Limbrel, are thought to be immune mediated. As nearly as we can determine, the incidence of abnormal LFTs with Limbrel is about

2-5%, though this is only an estimate since we suspect that many are not reported to us. This is comparable to most NSAIDs which give an incidence of up to 15% abnormal LFTs in their package inserts. The overwhelming majority of these patients are asymptomatic though occasionally patients may complain of diarrhea, other abdominal distress, dark urine or fever. The LFT abnormalities are generally minor elevations (2-4x normal) mostly of transaminases, occasionally alkaline phosphatase, and are found on routine laboratory evaluations or those specifically done to monitor for Limbrel liver effects. From 2004 to date, Primus has received 65 cases of elevated LFTs. Very rarely we have received reports of more serious liver abnormalities including jaundice (n=13). In every case known to us, patients have recovered without residua within 2-6 weeks depending on the severity of the liver abnormalities. No treatment is indicated except for discontinuance of Limbrel. Primus strongly recommends that patients starting Limbrel have their LFTs checked in 4-6 weeks, then at regular intervals thereafter.

It is noteworthy that both of these adverse events tend to occur early in the patient's exposure to Limbrel. Hypersensitivity pneumonitis generally occurs within 1-3 weeks, though we have one report of a 2-month delay from start of dosing to symptoms. Elevated LFTs generally occur within the first 2-3 months of therapy. Hence, patients who have been on Limbrel therapy for several months are very unlikely to develop either of these complications which may be an important consideration for those patients in specific need of Limbrel because they either cannot tolerate or have comorbidities that preclude the use of NSAIDs.

We are diligently working with the FDA, and highly-respected independent experts, to try to identify and eliminate the offending factor responsible for the hypersensitivity pneumonitis. Until further notice, we have discontinued our new patient program. We recommend discussing the potential adverse events of Limbrel (as a medical food product) compared to NSAIDs, or other therapeutic choices, with patients for whom you are considering prescribing Limbrel. If you make the decision to prescribe Limbrel, then we recommend that the patient be carefully monitored for the first three months of use, with continued periodic monitoring thereafter. We are also in the process of updating our website (limbrel.com) and other patient and professional materials to reflect our expanded experience.

Please feel free to contact me directly at 480-483-1410 or rlevy@primusrx.com if you have further questions or would like to discuss any of these issues.

We appreciate your support of Limbrel and your attention to this safety update.

Sincerely,

Robert M. Levy, M.D.

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Director of Clinical Development