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Subject: Adverse Event Reporting Evaluation
Exponent Project No. 1107976.000 E0T1

Dear Mr. Siegner:

As per your request, Exponent has reviewed the U.S. Food & Drug Administration [FDA] Health Hazard Evaluation [HHE], dated November 17, 2017, involving the medical food Limbrel [flavocoxid] produced by Primus Pharmaceuticals in Scottsdale, Arizona (see attachment). The review was conducted by a multidisciplinary team consisting of Chester C. Clarke, M.D., M.P.H., M.S., a preventive medicine specialist; P. Michael Bolger, Ph.D., D.A.B.T., a board-certified toxicologist and former head of the FDA CFSAN chemical risk assessment staff, and Arthur J. Miller, Ph.D., C.F.S., a former FDA CFSAN senior scientist. Our comments about the HHE are as follows:

Section 4, "Nature of the Problem"

It was noted that FDA had received a total of 194 adverse event reports concerning Limbrel from January 1, 2007 to November 9, 2017. Of these, 57 contained sufficient information to discern if Limbrel was associated with various adverse events such as "hepatitis, liver failure, and hypersensitivity pneumonitis, a form of respiratory failure." Thirty of the 57, according to the report, "contained sufficient information to use the causality assessment method to determine the likelihood that an association between the consumption of Limbrel and the adverse events existed." The report also noted that there were no known fatalities.

Hypersensitivity pneumonitis [HP] is not a form of respiratory failure. Respiratory failure is an extremely serious condition indicating the patient is not able to breathe independently, and the standard of care is to be placed on a ventilator. This condition is defined by a PaO2 of less than 60 mm Hg or a PaCO2 greater than 45 mm Hg or a combination of both [PaO2 and PaCO2 are arterial blood gas measurements][1]. Acute respiratory failure is an acute event while chronic respiratory failure occurs gradually over time as the respiratory reserve of the lung is chronically diminished[1]. Some examples of causes of acute respiratory failure include pulmonary edema, pulmonary embolus, and pneumonia; some examples of causes of chronic respiratory failure include asbestosis, emphysema, and idiopathic pulmonary fibrosis.

Virtually all respiratory adverse event reports that we are aware of are consistent with acute hypersensitivity pneumonitis, not complete respiratory failure. They include (1) those cases provided by FDA under FOIA and (2) those cases of respiratory-related adverse event descriptions reported directly to Primus. Furthermore, (3) evidence was provided to Exponent about discussions by reporting case patients and physicians to the Primus Medical Director.

Hypersensitivity pneumonitis is an allergic respiratory disease that has been described as having acute, subacute, and chronic forms[2,3]. The acute form tends to be self-limited with signs and symptoms clearing in 24 to 48 hours with avoidance of the exposure although steroids are often prescribed[2]. The chronic form, after the lung has undergone interstitial fibrosis, has been described as causing respiratory failure[2,4].

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[1] Lilly C, E.P. Ingenito, and S.D. Shapiro. 2005. Respiratory failure. p. 1588-1591. *In.* Kasper D.L. *et al.* (eds), Harrison's principles of internal medicine, 16th ed New York, McGraw-Hill.

[2] Selman M. 2003. Hypersensitivity pneumonitis. p. 452-484. *In.* Schwarz, M.I. and T.E. King Jr (eds), Interstitial lung disease, 4th ed. London, BC Decker, Inc.

[3] Kurup, V.P., M.C. Zacharisen and J.N. Fink. 2005. Hypersensitivity pneumonitis. *Indian Journal of Chest Disease & Allied Sciences*. **48:**116-128.

[4] Lima, M.S., E.N.A.M Coletta, R.G. Ferreira, D. Jasinowodolinski, J.S.O. Arakaki, S.C.S. Rodrigues, N.A.N.S. Rocha and C.A.C. Pereira. 2009. Subacute and chronic hypersensitivity pneumonitis: histopathological patterns and survival. *Respiratory Medicine.* **103:**508-515.

Thus, generalizing the actual reported cases related to respiratory adverse events can cause a misleading understanding of the likelihood, severity, and reversibility of this category of adverse events which are key elements used to assess the potential public health impact of this situation.

Similarly, based on our review of adverse event reports, the nature of liver adverse events associated with the use of Limbrel could be more accurately described as reversible compromised liver function. Acute liver failure is defined as the rapid development of hepatocellular dysfunction, specifically coagulopathy and mental status changes (encephalopathy) in a patient without known prior liver disease. It should also be noted that acute liver failure [ALF] is also an extremely serious condition defined by jaundice and hepatic encephalopathy. Acute liver failure is the rapid appearance of severe complications after the first signs of liver disease (e.g., jaundice), which indicates that the liver has sustained severe damage which is defined as loss of function of 80–90% of liver cells. Other complications include impaired protein synthesis as measured by the levels of serum albumin and the prothrombin time in the blood. The development of ALF is ultimately predictive of prognosis. The underlying cause is the other significant determinant of outcome. The main features of acute liver failure are rapid-onset jaundice, weakness, and ultimately changes in mental status that can begin as mild confusion which may progress to coma[5,6].

Our assessment is that these adverse events appear to be idiosyncratic reactions to using Limbrel. There is not a consistent pattern of age, sex, race, concomitant drug use or any other factor driving this reaction other than nearly all adverse reactions occurred in a small number of new patients.

[5] O'Grady, J.G. 2005. Acute liver failure. *Postgraduate Medical Journal*. **81**:148–154.
[6] Sleisenger, M. H., M. Feldman, L.S. Friedman and L.J. Brandt. 2010. Sleisenger and Fordtran's gastrointestinal and liver disease: Pathophysiology, diagnosis, management. 9th ed. Philadelphia: Saunders/Elsevier.

Section 5, "Have any adverse reaction reports or other indications of injuries or diseases been reported relating to this problem?"

The box "Yes" is checked. The report indicated that there were 14 patients diagnosed with drug-induced liver injury [DILI] and 21 patients diagnosed with HP. The report noted that "the fact Limbrel was associated with 21 cases of HP and 14 cases of DILI is significant because if not treated early, HP and DILI might cause irreversible damage to the lungs or liver."

Upon the Freedom of Information (FOI) request, FDA released MedWatch records in their possession. The records consisted of 69 individual cases, of which 16 were related to the liver, 24 were related to the respiratory system, and 6 were related to both. There were 5 cases that mentioned jaundice. There was only one case that noted liver failure and this case had no recorded evidence of having jaundice, although that was possible with a bilirubin of 3.3, no evidence of encephalopathy or a coagulopathy and was not noted have been placed in an ICU. Consequently, it would appear that this patient did not in fact have liver failure and to reinforce that opinion, after stopping the product, the patient's bilirubin returned to normal. There was one case noted to have been admitted for respiratory failure, but there was no mention of intubation or ICU care; PaO2 or PaCO2 levels were not reported as well. There were four cases where the oxygen saturation levels might indicate respiratory failure; however, there was no mention of respiratory failure, of the arterial blood gas results, ICU care, or intubation. In all records that were received, there was no mention of permanent or chronic illness and, as noted above, no fatalities. Most of the cases follow a very similar tract. Once the person becomes ill they go to their primary care physician [PCP] or the hospital and then once the ingestion of Limbrel is stopped they begin to return to normal. The important point is that the person stop taking Limbrel once they become ill. The records received show no evidence that any patient suffered irreversible damage of the liver or the lung.

In the four articles referenced in the FDA HHE: Youssef et al. (2010); Panduranga et al. (2013); Chalasani et al (2012); and Alsamman et al (2014), none of the patients described had a diagnosis of liver or respiratory failure and, according to the authors, none had permanent lung or liver damage[7,8,9,10]. The LiverTox database of the National Library of Medicine also referenced by the HHE, noted that "most cases have been moderate in severity and no instance of acute liver failure or death has been reported[11]. Resolution upon stopping flavocoxid has occurred in 1 to 3 months…No instances of acute liver failure or chronic liver failure have been linked to flavocoxid use and all cases have been self-limited, without subsequent chronic hepatitis or vanishing bile duct syndrome."

Section 7, "Adverse Reaction Information: What are anticipated health effects associated with this problem?"

The report listed several adverse events and noted that "The most serious adverse events associated with the use of Limbrel include descriptions of hepatitis, liver failure, and hypersensitivity pneumonitis, which may result in respiratory failure. Both of these types of events are potentially life-threating." As noted above, one case was noted to have respiratory failure and it is unclear if indeed that was a true case of respiratory failure. Other cases were possible, but not specifically diagnosed per the records received. Again, as noted above, there is no indication that anyone had liver failure.

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[7] Youssef, J.G. and R. Tomic. 2010. Limbrel (Flavocoxid) as cause of hypersensitivity pneumonitis. *Chest.* **138.**

[8] Panduranga, V., J. Atienza, A, Kumar and M.L. Metersky. 2013. Hypersensitivity pneumonitis due to flavocoxid: are corticosteroids necessary? *Connecticut Medicine*, **77**:87-90.

[9] Chalasani, N., R. Vuppalanchi, V. Navarro, R. Fontana, H. Bonkovsky, H. Barnhart, D.E. Kleiner, and J.H. Hoofnagle. 2012. Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: A case series. *Ann Intern Med*. **156**:1-7.

[10] AlSamman, S., and S. Mallick, 2014. Flavocoxide (Limbrel) induced hypersensitivity pneumonitis [abstract]. *J. Hospital Medicine.* Available at: http://www.shmabstracts.com/abstract/flavocoxide-limbrel-induced-hypersensitivity-pneumonitis/. Accessed on: 10 January 2018.

[11] National Institute of Diabetes and Digestive and Kidney Diseases. 2018. LiverTox—Clinical and Research Information on Drug Induced Liver Injury, U.S. National Library of Medicine—National Institutes of Health, Bethesda, Maryland. Available at: https://livertox.nih.gov/Flavocoxid.htm. Accessed on: 11 January 2018.

Section 9, "Is the problem easily identified by the user or are there other mitigating circumstances that lessen the probability that the product will be consumed?"

"No" is checked. The medical issue here is the continued consumption of the product. When the patient stops taking the product, the illness, whether liver or respiratory related, regresses and stops. The patient stops the medication usually because of the warning signs of the adverse effect. In other cases, the prescribing physician instructs the patient to stop use. So, for the initial consumption of the product the correct answer is "No,' but for the continued consumption of the product when the product has caused an adverse event the correct answer is "Yes." This is particularly the case because of the uniqueness of the patient population of concern. The only individuals who consume Limbrel are those who are under a physician's care for treatment of osteoarthritis [OA] for which Limbrel is prescribed as part of their therapeutic regime. Irrespective of Limbrel, the standard of medical care is for physicians to monitor liver and lung function in their OA patients. Any physician who prescribes Limbrel is aware of possible side effects and will so inform the patient under their care as to potential side effects. Under this set of circumstances and because of the uniqueness of the at risk population, the notion that the problem would not be easily identified by the patient and the physician who is treating them is simply not tenable, given the facts.

Section 10, "What is the hazard associated with the use of the product?"

Three items are checked: "life threatening (death has or could occur"; "Could possibly result in permanent impairment of a body function or permanent damage to a body structure"; and "Necessitates medical or surgical intervention (including hospitalization) to preclude or reverse permanent damage to a body structure or permanent impairment of a body function." A comment noted, "There are no reported related fatalities in FDA MedWatch. However, 'life-threatening' is included as hepatitis and hypersensitivity pneumonitis, if left untreated, might result in mortality." Again, the medical issue is that the patient stop taking the product. As Panduranga et al point out in their article titled "Hypersensitivity Pneumonitis Due to Flavocoxid: Are Corticosteriods Necessary?": "The most important aspect of management is

identification of the inciting agent so that avoidance measures can be implemented. In this patient, we identified and discontinued the inciting agent, which led to complete resolution of the condition[8]." Chalasani et al clearly did not state or imply that LFT's were not monitored in OA patients[9]. Virtually all physicians prescribing OA medications would confirm that their patients definitely would stop use of an OA product if instructed by their physician due to a liver safety concern. The third option in the section, "Necessitates medical or surgical intervention (including hospitalization) to preclude or reverse permanent damage to a body structure or permanent impairment of a body function" is the appropriate item that should be checked.

Section 11, "What is the probability of each adverse event occurring, as specified in Item 10?"

The item "Likely to occur (reasonable probability of occurrence)" has been checked. The HHE indicated that they had received 194 MedWatch reports from January 1, 2007 to November 9, 2017 and determined that for 30 of the 194 there existed the "likelihood that an association between the consumption of Limbrel and the adverse events existed." According to data received by Exponent, covering January 1, 2007 to October 31, 2017, 1,973,000 prescriptions and physician samples of Limbrel were dispensed. The MedWatch system is a passive surveillance system which could underestimate the number of adverse events. But, given FDA's data, the occurrence rate of adverse events would be 30/1,973,000 or (1.5 per 100,000). Therefore, even if these events were under-reported the box that should be checked is "Might occur (remote probability of occurrence)."

Conclusion

The report noted, "There is reasonable probability that if a consumer were to consume this product, s/he may experience any one of the aforementioned adverse events that include but are not limited to elevated liver function tests, jaundice, nausea, fatigue, gastrointestinal discomfort, fever, chills, headache, cough, chronic bronchitis, hypoxemia, shortness of breath or trouble breathing, and weight loss. The consequences of delayed treatment of conditions such as liver failure or respiratory failure are potentially life-threatening."

Indeed, it is true that the consequences of delayed treatment of either liver failure or respiratory failure are potentially life-threatening. As noted above, there is no indication from the MedWatch reports that any person had actual liver failure and it is unclear and in fact unlikely that anyone had respiratory failure. There are reports of liver injury as noted by elevated liver enzymes and bilirubin and clinical jaundice but in the MedWatch records received, no one had hepatic encephalopathy and no one had a coagulopathy, the basis for the diagnosis of liver failure. In addition, no one was noted to have a PaO2 less than 60 mm Hg or a PaCO2 greater than 45 stated in the records received, the basis of the diagnosis of respiratory failure, and no one was noted to have been intubated and placed on a ventilator, frequent practice for patients in respiratory failure. If indeed someone was reporting a case of respiratory failure, one would expect the diagnosis along with supporting information regarding the blood gas results. Therefore, in our view, the HHE is fundamentally flawed. It bases the conclusion that Limbrel may cause life threatening adverse effects on the assumption that events that we find no, or at best weak evidence of ever having occurred over 13+ years of use.

Further, the conclusion that there is a "reasonable probability" of an adverse outcome upon consumption of this product is not consistent with the facts identified above. The available evidence clearly indicates that the incidence of adverse outcomes in the population of concern is low. In addition the at-risk population is very unique. The population is not a population of general consumers who acquire the product on their own initiative, but rather only those patients who suffer from osteoarthritis and are under the care of physicians who prescribe the product. Physicians who are treating such patients would be aware of possible side effects and would so inform their patients, which is normal practice as part of appropriate patient care. Patients who have been on Limbrel for more than 3 months, which represents most Limbrel users, appear to have no risk of liver or respiratory complications. The only possible and appropriate conclusion should have been "might occur (remote probability of occurrence)" which would have been consistent with the available information outlined above.

Limitations

The scope of services performed during this evaluation or recommendation presented herein are at the sole risk of the user. The findings, conclusions, and recommendations formulated during this assessment are based solely on information supplied by the client. If new data become available, or there are perceived omissions or misstatements in this letter regarding any aspect of those conditions, we ask that they be brought to our attention as soon as possible so that we have the opportunity to fully address them.

If you have any questions or require additional information, please do not hesitate to contact me at (949) 242-6009 or amiller@exponent.com.

Sincerely,

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