CFSAN HEALTH HAZARD EVALUATION

HHE # 9752 ***Date Assigned*** November 17, 2017 ***RES#*** _____

Section A. Incident Summary (to be completed by requesting CSO)

1. **PRODUCT INFORMATION** (Include relevant lot information if appropriate.)
   Limbrel (flavocoxid 500mg) Medical Food Product, 60 Capsules

2. **FIRM INFORMATION** (Include supplier information if appropriate and note if domestic or foreign.)
   Primus Pharmaceuticals, Scottsdale, AZ (Domestic)

3. **SOURCE OF PROBLEM**
   ☐ undeclared allergen
   ☐ microbial contamination – specify
   ☐ presence of foreign bodies
   X other – specify: Adverse event reports describing injury to the liver and lung.

4. **NATURE OF PROBLEM** (What happened to create the hazard/ problem? What is the extent of the problem and/or how was the problem identified? Include GMP, labeling errors, consumer complaints, etc.)

   Limbrel is marketed by Primus Pharmaceuticals (Scottsdale, AZ) as a medical food for osteoarthritis. The product is described as a prescription product containing flavocoxid (a proprietary blend of baicalin and catechin) and is derived from medicinal plants. Sporadic reports of adverse events have been received by the Agency in the past. Recently, however, there has been an increase in the number of reports, specifically 6 from late August through October 2017. Most of the recent reports have cited serious adverse events, specifically drug-induced liver injury and hypersensitivity pneumonitis. This triggered a re-review of the situation which drew on multiple information sources. This comprehensive review shows that from January 1, 2007 to November 9, 2017, FDA received a total of 194 adverse event reports regarding Limbrel. Of these cases, 57 contained sufficient information to analyze in detail whether Limbrel was associated with an adverse event including hepatitis, liver failure, and hypersensitivity pneumonitis, a form of respiratory failure. The 57 consumers included 43 females, 13 males, and one of unknown gender; ages ranged from 32 to 89 years old. Thirty of the 57 MedWatch reports 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. No known fatalities have occurred.

5. **Have any adverse reaction reports or other indication of injuries or diseases been reported relating to this problem?**
   [ ] No [X] Yes – Please see attached report, section 4 and below

The most serious health effects associated with consumption of Limbrel included drug-induced liver injury (DILI) and hypersensitivity pneumonitis (HP). Fourteen patients were diagnosed with DILI and 21 patients were diagnosed with HP. Three of the 14 liver adverse events were

assessed as *likely* and 9 were ranked as *possibly* with respect to whether the adverse event was associated with the consumption of Limbrel.[1] (For two of the reported events, there was insufficient information to make a determination.) Five of the patients diagnosed with DILI were hospitalized. Of the 21 consumers with HP, 5 were assessed as *certain*, 4 as *likely*, and 9 as *possibly* with respect to whether the adverse event was associated with the consumption of Limbrel. (For 3 of the reported events there was insufficient information to make a determination.) Sixteen of the patients diagnosed with HP were hospitalized.

Of the 57 reported adverse events, 27 (47%) could not demonstrate a temporal relationship between consumption of Limbrel and adverse event while 30 (53%) contained enough information to support the conclusion that Limbrel was associated with an adverse event. Four of those adverse events involving the liver included a biopsy that supported the diagnosis of DILI. Seventeen of the HP cases included one or more of the following: laboratory studies, imaging studies, a biopsy, or information indicating that the consumer ingested Limbrel on several occasions and experienced the same adverse event each time s/he ingested Limbrel (i.e., showed evidence of relapse on rechallenge with Limbrel). The fact that 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.

As noted above, FDA has received sporadic reports of adverse events dating from 2007, but the magnitude was not apparent until a thorough re-review that drew from several different sources and included the old cases, other newly identified cases from prior years plus the new cases that prompted the re-review. Of these latest reports, a significant portion documented liver injury and/or HP and are considered serious.

6. REFERENCE HHEs (Using the CFSAN HHE database, please summarize any related precedents. Please include reference numbers or copies of supporting precedent cases.)

HHE #	Date Signed	Hazard Identified

No known reference HHEs were found.

Section B. Health Effects Review (to be completed by HHEB member)

7. ADVERSE REACTION INFORMATION

What are anticipated health effects associated with this problem? (i.e., consumption of the product and/or specific ingredients) Include narrative and please describe severity. Explain and cite literature references when applicable.

Adverse events reported by persons who ingested Limbrel who experienced hepatitis, liver injury, or hypersensitive pneumonia described, among other findings, 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

[1] Based on Report of CIOMS Working Group V. Geneva, The Council for International Organizations of Medical Sciences, 2001

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 types of events are potentially life-threatening.[2] [3] [4] [5] [6]

8. AT RISK POPULATION

Are there certain population(s) of consumers most likely to use and/or be most at risk from exposure to this problem or hazard? (Please list all that apply and provide additional explanation if necessary.)

[ ] No – the general population is at risk
[X] Yes – check all that apply
_____ Infants
_____ Children
_____ Pregnant women, nursing women, or women of childbearing age
X____ Elderly consumers
_____ Individuals with allergy/intolerance to (food/product)
_X___ Immunosuppressed individuals
_____Medical conditions (e.g., diabetes, celiac disease)
_X__ Other (please describe): all adult patients diagnosed with Osteoarthritis

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?
[X] No [ ] Yes – Provide explanation:

10. What is the hazard associated with use of the product? (Select one. If more than one is selected, please explain.)

_____X____ Life-threatening (death has or could occur)
_____X____ Could possibly result in permanent impairment of a body function or permanent damage to a body structure

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[2] Youssef JG, Tomic R Limbrel (Flavocoxid) as cause of hypersensitivity pneumonitis Chest 2010; 138(4_MeetingAbstracts:79A. doi:10.1378/chest.10821

[3] Panduranga V, Atienza J, Kumar A et al. Hypersensitivity pneumonitis due to Flavocoxid: are corticosteroids necessary? Conn Med. 2013 Feb;77(2):87-90.

[4] Chalasani N, Vuppalanchi R, Navarro V et al. Acute liver injury due to Flavocoxid (Limbrel), a medical food for osteoarthritis: a case series. Ann Inter Med. 2012 Jun 19;156(12):857-60, W297-300.

[5] https://livertox.nih.gov/Flavocoxid.htm

[6] Alsamman S, Mallick S, Flavocoxid (Limbrel) Induced Hypersensitivity Pneumonitis. Journal of Hospital Medicine. 2014; 9 (suppl. 2)

_____X____ Necessitates medical or surgical intervention (including hospitalization) to preclude or reverse permanent damage to a body structure or permanent impairment of a body function
_____ Temporary or reversible (without medical intervention)
_____ Limited (transient, minor impairment or complaints)
_____ No adverse health consequences
_____ Hazard cannot be assessed with the data currently available

*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.

11. What is the probability of each adverse event occurring, as specified in Item 10?
(If more than one item is selected below, specify the corresponding health hazard.)

_____ Highly likely to occur (every time the product is used)
_X___ Likely to occur (reasonable probability of occurrence)
____ Might occur (remote probability of occurrence)
_____ Unlikely to occur
_____ Unknown (please explain):
_____ Not applicable

Conclusion:
There is a 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.

SIGNATURES

Kerri Harris -S

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Date: November 22, 2017

Requested by: Kerri Harris-Garner, Ph.D.
Consumer Safety Officer

Andrea Lotze -S

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Medical Officer
Health Hazard Evaluation Board Member

Karl C. Klontz -S

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Linda M. Katz, M.D., M.P.H., F.A.C.P.
Acting Chief Medical Officer
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