LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.
700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D.C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

A. WES SIEGNER, JR.
Direct Dial (202) 737-4289
ASiegner@hpm.com

December 20, 2017

BY E-MAIL
[Steven.Porter@fda.hhs.gov]

CDR Steven E. Porter
Division Director
Division of Pharmaceutical Quality Operations IV
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2445

Dear Mr. Porter:

I am responding on behalf of Primus Pharmaceuticals, Inc. (Primus) to the letter that Primus received on December 19 from Melinda Plaisier, Associate Commissioner for Regulatory Affairs, Food and Drug Administration (FDA). She is copied on this letter.

For nearly 14 years, Limbrel® has been marketed as a medical food dispensed by prescription and under physician supervision, with over 2 million packages sold and sampled in that time to an estimated 450,000 patients. Limbrel is used primarily by rheumatology and pain management specialists in osteoarthritis (OA) for patient populations that are not appropriate for NSAIDs and want to avoid opioids. Primus has diligently followed up on adverse events (AEs) it has received and has consistently reported to FDA any serious adverse events.

Limbel does meet the statutory definition of a medical food as set forth in the Orphan Drug Act. In fact, Limbrel has been referenced as such in many peer-reviewed nutritional, regulatory, clinical, and scientific peer-reviewed articles. Limbrel also is supported by a body of clinical and scientific evidence likely unmatched by other medical food products. FDA has clearly been aware of Limbrel as a medical food by prescription for well over a decade. Until this month, FDA has considered Limbrel to be a medical food, not a drug, as is shown by FDA's collection of AEs for Limbrel in FDA's Center

for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) database, as well as through FDA's interactions with Primus and patients in addition to manufacturing GMP inspections over the years.

Historically, both FDA and Primus have received very low numbers of reports of acute hypersensitivity pneumonitis (AHP) and elevated liver function tests (LFTs). These events are known to be, and in the case of Limbrel have been, temporary and medically reversible. Both of these adverse events have been described in the product insert since 2010, as well as in a "Dear Doctor" letter dated May 2010. Primus' understanding that these events are not life threatening has been and continues to be confirmed by medical experts, by the medical literature, and by the complete reversal of the adverse effects on termination of Limbrel use.

From the November 8th first visit by FDA asking for copies of Limbrel's adverse events, Primus has fully cooperated with FDA even to the point of disclosing our highly-confidential formulations, on a voluntary basis, without a court order. Without notice to Primus, FDA issued a surprising safety alert on November 21, calling these events "potentially life threatening." Primus immediately began to conduct independent safety reviews of Limbrel with former senior FDA food scientists and toxicologists at the widely respected consulting group Exponent. Primus requested that these experts be provided with the 194 AEs (note: these account for all AEs, most of which are not serious) that FDA cited as a basis for the agency's concern.

Despite FDA's claim that Limbrel causes potentially life-threatening adverse events, FDA would not share its cases with Primus and instead FDA informed Primus that the company would need to file a Freedom of Information Act (FOIA) request. Primus did so on November 22. Even though FDA has to-date not provided copies of the 194 AE reports for this review, Primus has proceeded with the promised independent Limbrel safety review. Primus has also informed Limbrel prescribers and patients of FDA's concerns, educated physicians about AHP and LFTs (as was done in 2010 stated above, and again in November of this year), and stopped its new patient program.

Unexpectedly, on November 30, FDA informed Primus during a telephone conference that the agency had conducted a formal health hazard evaluation (HHE), which (pursuant to FDA's regulations) is required agency practice before FDA classifies a recall. Presumably, the HHE would set forth FDA's rationale for FDA's finding that Limbrel has potentially life-threatening effects. FDA then requested that Primus

voluntarily recall Limbrel, and gave Primus 24 hours to respond. Primus then requested a copy of FDA's HHE in order to assess the basis for FDA's recall determination, and Primus again requested copies of the related AE reports. FDA advised Primus to file another FOIA request for the HHE, which Primus did on December 1. To-date, Primus has twice been informed by FDA that these FOIA requests would be expedited, but Primus has yet to receive any AE reports or the HHE. Therefore, Primus is unable to assess FDA's basis for the safety alert and the two requests for recall, and is unable to determine why FDA's HHE fundamentally differs from what is known about AHP and LFTs from the medical literature and from the advice that Primus has received from experts.

Primus has consistently been advised by independent experts, some with years of experience in hundreds of patients using Limbrel, that the AEs at issue are not life-threatening, and Primus has shared a number of these written opinions with FDA. I have again provided copies of these written opinions, and several additional written opinions, with this letter.

The medical opinions shared with FDA clearly establish that, given the absence of alternatives to Limbrel, the health of patients suffering from OA will be seriously compromised if FDA forces them to stop using Limbrel. I urge the senior officials at FDA to read the opinions of these specialist medical professionals, as they make clear the importance of Limbrel to patients suffering from OA. Due to the public health consequences for these patients, we are repeating our plea to FDA to not make any further decisions on Limbrel until after consulting with these experts, who have real world experience treating OA generally and with the management of OA using Limbrel specifically. For perspective, in FDA's own FAERs database, between 4% and 12% of adverse events reported for leading NSAIDs (each) are death.

Both Primus and independent experts at Exponent and in medical practice are continuing to evaluate the AEs to which Primus has access. With no ability to see FDA's rationale for determining that the AHP and LFT events are life threatening, Primus at this time has no basis to disagree with the conclusions that its experts have reached with respect to the safety of Limbrel, or to agree with FDA's assessment that the events observed for Limbrel are life-threatening.

The written opinions of the physicians with extensive experience with Limbrel show that it is in the best interest of public health that physicians and their patients

continue to have access to Limbrel. The following quotes from several of these physicians establish that Limbrel is safe and provides an important option for OA:

> Recalling or advising consumers not to use Limbrel is the fastest way possible to dramatically increase the amount of narcotics used in my pain medicine practice. This is a reality of medicine practiced in the trenches. To return to academics, there is statistical suggestion that Limbrel has lowered narcotic use nationwide that warrants further investigation.
>
> In comparison to other treatment options, Limbrel has the cleanest safety profile for the special population that I treat. This is why Limbrel is an important part of treatment for OA, because of its low incidence of side effects and its effectiveness for my most complex patients. If Limbrel is forced off the market, I will again go back to limited options for my cardiovascular patients. This will leave some of my patients to deal with the pain of OA with nowhere to turn.
>
> My patients, on the whole, have done well on Limbrel in regard to pain relief. Although it does take a little more time to obtain pain relief than NSAID's and opioids, just informing the patients of this helps to alleviate anxiety regarding whether it is working or not. I try to use Limbrel as a first-line pain reliever whenever I am able because of its effectiveness and safety profile. In summary, it is important for my patients to have the availability of Limbrel. There is nothing else I could prescribe that would fill the void if Limbrel were taken off the market.
>
> I am a patient and have been on Limbrel for 7 yrs. I have also been a rheumatologist for 30 yrs. [E]ven with the events reported by FDA, issuing a safety alert suggesting that physicians remove their patients from Limbrel . . . without taking into consideration the other options that exist and their consequences only harms public health as well as the FDA's credibility. For the sake of transparency and the goal of making important public health decisions based on all of the facts, I request that FDA revisit its safety alert on Limbrel and if an error has occurred, that it be corrected immediately.
>
> As a Rheumatologist, my patient population involves high risk patients on anti-coagulation with chronic kidney disease and multiple co-morbidities. For these patients, Limbrel has provided benefit that otherwise could not be offered with NSAIDs. I have used Limbrel, with good results, in the majority of my patients. In my practice, I have patients start Limbrel QD. If they tolerate well, they advance to BID and we monitor these patients with LFT testing after two to three weeks starting the medication and every two or three months after. Keeping in mind, these patients are on multiple medications and some of them drink alcohol.

> If I find liver function abnormalities, I discontinue the therapy. I have not encountered hypersensitivity pneumonitis.
>
> I have placed many patients on this medical food with good clinical results. I have not had any adverse effects. Considering the opioid epidemic and problems with NSAIDS this is a very safe and effective alternative. Removing Limbrel from the market significantly limits the therapeutic alternatives and treatment for osteoarthritis.

By letter on December 18, FDA again requested that Primus recall Limbrel, and has requested for the first time that Primus also cease distribution of Limbrel. FDA again imposed a short 24-hour deadline and posted the December 18 letter on its website, all with the clear intent to force Limbrel from the market without ever disclosing to Primus, Primus' experts, or this law firm the basis for FDA's safety concerns. I had concluded from a call on FDA on Friday, December 15, that the written opinions from physicians expressing a critical need for continued access to Limbrel had convinced FDA that a meeting with Primus and these experts should be the next step, and I had no indication that FDA intended again to publicize a request for a recall. We were therefore completely surprised to receive this second recall request.

We were also surprised that FDA's "preliminary evaluation" of Limbrel's medical food status appeared to have somehow moved to a final determination of unapproved new drug status without ever reviewing Primus' extensive distinctive nutritional requirements analyses for OA that Primus offered to FDA during the November 30 call. Primus mistakenly thought on that call that FDA would be open to further discussions of the medical food status of Limbrel. We have experienced a complete lack of cooperation and transparency in our dealings with FDA with respect to Limbrel.

Congress intended to stimulate innovation in nutrition and patient care when it enacted the statutory definition of a medical food in 1988. If FDA and industry could work together and FDA be open to innovation, medical foods provide a great opportunity to advance public health while reducing total costs of care.

FDA has now taken action twice to undermine and effectively destroy the market for a product without providing notice of the basis for the agency's asserted public health concerns. FDA has used press releases to drive physicians and patients away from using Limbrel while depriving Primus of any ability to understand FDA's concerns or defend Limbrel from FDA's press attacks. Nonetheless, it is perhaps not too late for FDA to

rescue its credibility. FDA can do so by taking time to review the information and opinions Primus has provided to put FDA's concerns in the proper context of public health, responding to Primus' FOIA requests prior to rushing to judgment, meeting with Primus and experts to determine the best path forward, and discussing the distinctive nutritional requirements of OA with Primus and experts.

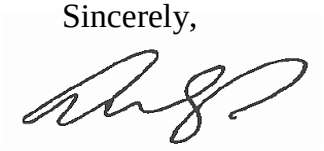
Despite FDA's actions, Primus' opinion remains that Limbrel is a legal medical food and that Limbrel's safety is exemplary when considered, as is appropriate, in the context of its intended use, as the written opinions that Primus has provided to FDA show. Nonetheless, in response to FDA's extraordinary actions against Limbrel, Primus is voluntarily taking the steps outlined below pending a meeting with FDA. Primus will:

- Immediately suspend manufacturing, promotion, and further shipments into the retail distribution system of the current Limbrel formulations;
- Quarantine all Limbrel retail stock currently in Primus' possession;
- Inform FDA as soon as possible after receipt of FDA's HHE and the AEs of Primus' decision whether to recall Limbrel that is currently in distribution.

Primus remains convinced that a meeting with FDA will be productive, in particular to discuss why Limbrel is a legal medical food to manage the metabolic processes of osteoarthritis patients. Primus remains willing to schedule a meeting with FDA as soon as practical in order to cooperate with FDA to find answers to the difficult treatment and management of OA patients who, as the attached physician letters show, have obtained significant benefits from Limbrel without life-threatening adverse events.

Primus and Hyman, Phelps, McNamara wish to work with FDA in a collaborative and transparent fashion in the best interest of public health.

Sincerely,



A. Wes Siegner, Jr.

AWS/dlw

cc (*by email*): Melinda Plaisier
Associate Commissioner for Regulatory Affairs
Don Ashley
Director, Office of Compliance, CDER
Michael Levy
Deputy Director, Office of Compliance, CDER