FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting
FDA White Oak Campus, 10903 New Hampshire Avenue Building 31 Conference Center
The Great Room (Rm. 1503), Silver Spring, Maryland
January 12, 2016

DRAFT QUESTIONS

1. Probuphine is a non-titratable product that provides a fixed plasma level of buprenorphine. The original studies raised concerns about the appropriateness of the dose for a broad population. The Applicant has specified a population, namely stable patients on a relatively low dose of sublingual buprenorphine, for whom they believe the dose provided by Probuphine is adequate.

   DISCUSSION:

   a. Discuss whether there is a population that would benefit from the use of Probuphine and how to define this population.

   b. If there is a population that would benefit from Probuphine, discuss whether the study entry criteria adequately define this patient population.

   c. Discuss whether the population studied reflected this population.

2. In general, occasional dose adjustments for patients on sublingual buprenorphine can be expected over time. The sponsor chose not to include rescue medication as an element of the responder definition because there was an expectation that patients would require little to no rescue medication. However, that was not the case, as rescue medication was used by a number of patients, some throughout the 6-month treatment period.

   DISCUSSION: Discuss whether use of rescue should be considered in defining a responder for a long-acting formulation of buprenorphine such as Probuphine, where the dose cannot be adjusted over time. If rescue should be part of the responder definition, should the use of rescue buprenorphine be differentiated based on the pattern or the frequency of rescue use over the 6-month treatment? Consider the following patterns of use:

   a. Use primarily after first initiating Probuphine

   b. Use throughout the 6-month period

   c. Use only at the end of the 6-month treatment period

DRAFT QUESTIONS (cont.)

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3. Customarily in opioid addiction treatment trials, there are many missing urine samples due to relapse and dropout from treatment. Because relapse is the most common reason for dropout, missing urine samples are assumed to be positive. However, in this study, the patients were stably abstinent from illicit drugs, and they were asked to provide only 10 samples over six months. Therefore, it was expected that there would be few missing samples, and that these could be missing for reasons other than relapse. Therefore, the strategy for imputation of missing data did not assume that all missing samples were positive. However, some situations arose in which it might be appropriate to assume that missed samples are indicators of illicit use.

   DISCUSSION: Discuss how missing or incomplete urine toxicology results should be considered when defining a responder. Consider the following:

   a. Patients who were completely lost to follow-up immediately after receiving the Probuphine implant

   b. Samples that were not collected due to:

      1. Missed scheduled visit

      2. Missed random sample visit

      3. Refused by patient

   c. Samples that were collected on schedule but were not analyzed in a timely fashion (out of stability window for the test)

4. The protocol-specified responder definition did not take rescue use into account, and employed an optimistic imputation strategy for missing urine toxicology results, yielding a responder rate of 96% vs 88% for Probuphine and sublingual buprenorphine, respectively. As you have seen, there are many different possible responder rates once these factors are taken into account.

   DISCUSSION: Discuss which of the various approaches to expressing a responder rate you think is most appropriate.

DRAFT QUESTIONS (cont.)

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5. Patients managed with buprenorphine may require dose adjustment over time. However, in clinical practice, unlike patients on sublingual buprenorphine, Probuphine-treated patients would not necessarily be seen for regular visits with buprenorphine dose adjustments.

   DISCUSSION:

   a. Discuss how the need for occasional supplemental doses will translate to clinical practice for patients treated with Probuphine. If patients need to have sublingual buprenorphine on hand in addition to Probuphine, discuss how these prescriptions will impact the product's ability to mitigate misuse, abuse, and accidental pediatric exposure.

   b. Some patients on Probuphine required supplemental sublingual buprenorphine only briefly after insertion of the implant, while others required it only at the end of the dosing period when plasma levels could have been falling. In contrast, some patients required ongoing supplemental dosing throughout the 6-month treatment period.

      Discuss whether the pattern of supplemental sublingual buprenorphine should be taken into consideration when deciding if Probuphine is effective and should be continued for a given patient **in clinical practice**. Discuss whether there is a pattern of sublingual buprenorphine use that should result in the discontinuation of Probuphine.

6. The Sponsor has provided information on a training and certification program to ensure that practitioners can safely insert Probuphine. However, the procedure of removing Probuphine after six months of implantation is not readily modeled for the purposes of training because there is development of fibrotic tissue around the implants.

   DISCUSSION: Discuss the steps the Sponsor should take to ensure that removals, including complicated removals, are performed appropriately.

7. The Sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) which consists of restricted distribution and a training/certification program for healthcare professionals who will insert and remove the product.

   DISCUSSION: Discuss whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse, and accidental overdose.

DRAFT QUESTIONS (cont.)

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8. **VOTE:** Based on the data presented and discussed today, do the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine (as defined during prior discussion)?

9. **DISCUSSION:** Comment on any further development or explorations, e.g. higher doses, the Sponsor should undertake