CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #	203858
Product Name:	Juxtapid (lomitapide)
PMR/PMC Description:	A juvenile animal toxicology study to evaluate the effects of lomitapide on learning, memory, behavior, coordination, growth, and long bone development with and without vitamin and essential fatty acid supplementation to determine whether any observed effects are due directly to lomitapide or secondarily to the inhibition of absorption of fat soluble vitamins and/or essential fatty acids. This study should be completed before any formal pediatric studies are initiated.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	07/15/2013
	Study/Trial Completion:	12/30/2013
	Final Report Submission:	06/15/2014
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

   The intended pharmacodynamic activity of lomitapide is to reduce LDL-cholesterol and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH). HoFH is a life-threatening condition with unmet medical need. A specific safety signal has not been identified indicating that pediatric patients will be more susceptible to drug-induced injury, but there are theoretical concerns regarding the inhibition of cholesterol synthesis and/or the absorption of fat soluble vitamins and essential fatty acids during childhood, which is an important age for neurological development as well as overall growth.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Lomitapide inhibits the activity of microsomal triglyceride transfer protein (MTP), which prevents very low density lipoprotein (VLDL)-cholesterol and chylomicrons from being synthesized in the liver and small intestine, respectively. Chylomicrons are important for the absorption of fat soluble vitamins and essential fatty acids from the diet. Individuals with abetalipoproteinemia, a rare autosomal recessive disease that results from an inactivating mutation of the MTP gene, develop several neurological disorders including mental retardation, developmental delay, dyspraxia, muscle weakness, slurred speech, progressive decreased vision, and balance and coordination problems. It is suspected that the neurological deficits derive from deficiencies in fat soluble vitamins and essential fatty acids; however, the effect of MTP inactivation on cholesterol synthesis could also have a contributing effect on neurological development. The goal of the required juvenile toxicology study is to evaluate whether the use of lomitapide during early childhood years has a negative impact on neurological function, including learning, memory, behavior, and coordination.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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