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)

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/BLA #	203858
Product Name:	Juxtapid (lomitapide)
PMR/PMC Description:	An assessment and analysis of spontaneous reports of malignancy, teratogenicity, and hepatic abnormalities in patients treated with Juxtapid (lomitapide). Specialized follow-up should be obtained on these cases to collect additional information on the events.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/30/2013
	Interim Report Submissions:	12/31/2014
		12/31/2015
		12/31/2016
		12/31/2017
		12/31/2018
		12/31/2019
		12/31/2020
		12/31/2021
		12/31/2022
	Study/Trial Completion:	12/01/2023
	Final Report Submission:	06/01/2024
	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

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Juxtapid (lomitapide) was granted an orphan drug designation for the treatment of HoFH. Known and potential safety concerns include small bowel and hepatic malignancies, teratogenicity, hepatic transaminase elevations, hepatic steatosis, and potentially hepatic fibrosis. Given the small population affected by this disorder (~1 in a million), the small number of patients studied, and the short duration of clinical trials, enhanced pharmacovigilance is required to generate additional data to better assess risks related to the long-term use of the drug.

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."

The paucity of long-term safety data on Juxtapid (lomitapide) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Juxtapid (lomitapide) is limited. The pre-clinical and clinical development programs revealed known and potential serious risks associated with Juxtapid (lomitapide) including small bowel and hepatic malignancies, teratogenicity, hepatic transaminase elevations, hepatic steatosis, and potentially hepatic fibrosis.

The goal of the enhanced pharmacovigilance study is to gather additional data to better assess risks related to the long-term use of the drug. The study will continue for a period of 10 years from the date of approval.

The enhanced pharmacovigilance program will include the following:

a) Active query of reporters to obtain additional clinical information related to reports of malignancy, teratogenicity, and hepatic abnormalities. The sponsor should actively query reporters for the following information:

(i) For reports of malignancy: cancer site, timing and duration of Juxtapid (lomitapide) exposure in relation to diagnosis, and other risk factors for the specific cancer.

(ii) For reports of teratogenicity: nature of the defect, timing and duration of Juxtapid (lomitapide) exposure during pregnancy, and other risk factors for congenital malformations

(iii) For reports of hepatic abnormalities: liver-related laboratory, imaging and pathology results, duration of Juxtapid (lomitapide) exposure, and other risk factors for hepatic abnormalities

b) Expedited reporting to FDA of all initial and follow-up reports of malignancies, teratogenicity, fatty liver, hepatic steatosis, and hepatic abnormalities with a serious outcome.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

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.

Enhanced pharmacovigilance program for reports of malignancy, teratogenicity, and hepatic abnormalities in patients treated with Juxtapid (lomitapide) for a period of 10 years from the date of approval to collect data that will be analyzed to better define these risks. The enhanced pharmacovigilance program includes the following: a) active query of reporters to obtain additional clinical information related to reports of malignancy, teratogenicity, and hepatic abnormalities; b) expedited reporting to FDA of all initial and follow-up reports of malignancies, teratogenicity, fatty liver, hepatic steatosis, and hepatic abnormalities with a serious outcome. Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

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)
Enhanced pharmacovigilance

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)

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/BLA #	203858
Product Name:	Juxtapid (lomitapide)
PMR/PMC Description:	A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia (HoFH) treated with Juxtapid (lomitapide) to evaluate known and potential serious risks related to the use of Juxtapid (lomitapide).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/30/2013
	Interim Report Submission:	12/31/2014
		12/31/2015
		12/31/2016
		12/31/2017
		12/31/2018
		12/31/2019
		12/31/2020
		12/31/2021
		12/31/2022
		12/31/2023
		12/31/2024
		12/31/2025
		12/31/2026
		12/31/2027
	Study/Trial Completion:	03/01/2028
	Final Report Submission:	09/01/2028
	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

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by mutations in the low-density lipoprotein (LDL) receptor gene and characterized by elevated plasma levels of LDL cholesterol (LDL-C) with normal triglycerides, tendon xanthomas, and premature coronary atherosclerosis. Juxtapid (lomitapide) was granted an orphan drug designation for the treatment of HoFH. Known and potential safety concerns include small bowel and hepatic malignancies, hepatic transaminase elevations, hepatic steatosis, and hepatic fibrosis, teratogenicity, and major adverse cardiovascular events. Given the small population affected by this disorder (~1 in a million), the small number of patients studied, and the short duration of clinical trials, a postmarketing registry is required to generate additional person-years of exposure to assess risks related to the long-term use of the drug.

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."

The paucity of long-term safety data on Juxtapid (lomitapide) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Juxtapid (lomitapide) is limited. The pre-clinical and clinical development programs revealed known and potential serious risks associated with Juxtapid (lomitapide) including hepatic transaminase elevations, hepatic steatosis, hepatic fibrosis, small bowel and hepatic malignancies, teratogenicity, and major adverse cardiovascular events. The goal of the registry is to generate additional person-years of exposure to assess these and other serious risks related to Juxtapid (lomitapide) use.

The registry will include a sample of patients prescribed Juxtapid (lomitapide) and followed for 10 years.

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
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  ☐ Analysis using pharmacovigilance system?
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  ☒ 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?
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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.

The paucity of long-term safety data on Juxtapid (lomitapide) remains a concern. Because of the rarity of HoFH, the availability of patients and person-years of exposure that contribute to our current understanding of the safety of Juxtapid (lomitapide) is limited. The pre-clinical and clinical development programs revealed known and potential serious risks associated with Juxtapid (lomitapide) including hepatic transaminase elevations, hepatic steatosis, small bowel and hepatic malignancies, teratogenicity, and major adverse cardiovascular events. The goal of the registry is to generate additional person-years of exposure to assess these and other serious risk related to Juxtapid (lomitapide) use.

The registry will include a sample of patients prescribed Juxtapid (lomitapide) and followed for 10 years to describe the following:

- Patient age, sex, and race
- Country of treatment
- Cardiovascular history
- History of apheresis
- Other medical history
- Concomitant medications, including start and stop dates
- Use of dietary and vitamin supplements
- Use of contraception by females receiving Juxtapid (lomitapide) , including type
- Juxtapid (lomitapide) dose, duration of use, start date, discontinuation date, reasons for discontinuation, person-years of exposure
- Liver enzyme monitoring frequency
- Serum lipid levels

Data to be provided should include incidence rates for the following outcomes of interest:

- Death and causes of death
- Major adverse cardiovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, unstable angina, and revascularization procedures)
- Malignancies, including small bowel and hepatic neoplasms
- Hepatic adverse events including hepatic transaminase elevations with and without bilirubin elevations, hepatic steatosis, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hepatic fibrosis
- Exposed pregnancies and outcomes of exposed pregnancies

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
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☐ 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
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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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/s/

AMY G EGAN
12/20/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)
Division of Consumer Drug Promotion (DCDP)

****Pre-decisional Agency Information****

Memorandum

Date: December 12, 2012

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer
Division of Professional Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer, DCDP
Division of Consumer Drug Promotion (DPDP), OPDP

Subject: NDA 203858
OPDP labeling lomitapide mesylate, capsules for oral use

In response to DMEP's November 27, 2012, consult request, OPDP has reviewed the proposed draft package insert (PI) and medication guide for lomitapide mesylate, capsules for oral use.

OPDP comments on the proposed draft PI are based on the version sent via from Kati Johnson (RPM) email on December 6, 2012. OPDP's comments on the proposed draft medication guide are based on the version sent via email from Sharon Williams (DMPP) on December 11, 2012.

Comments regarding the proposed draft PI and medication guide are provided in the marked versions below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the proposed draft PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the proposed draft medication guide, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDRA Y JONES
12/12/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**November 14, 2012**
To:	Mary Parks, MD, Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	(lomitapide mesylate)
Dosage Form and Route:	Capsules
Application Type/Number:	203858
Applicant:	Aegerion Pharmaceuticals

1 INTRODUCTION

On February 29, 2012 Aegerion Pharmaceuticals submitted an original New Drug Application (NDA) indicated for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as adjunct to a low-fat diet and other lipid-lowering therapies (LLT).

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for lomitapide mesylate capsules.

The Risk Mitigation and Evaluation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DMEP by DRISK under separate cover. The MG for lomitapide mesylate capsules is outside of the REMS.

2 MATERIAL REVIEWED

- Draft lomitapide mesylate Medication Guide received on February 29, 2012 and received by DMPP on November 1, 2012.
- Draft lomitapide mesylate Prescribing Information (PI) received on February 29, 2012, revised by the Review Division throughout the current review cycle and received by DMPP on November 1, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG are consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON W WILLIAMS
11/14/2012

MELISSA I HULETT
11/14/2012

LASHAWN M GRIFFITHS
11/14/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: November 6, 2012 **Date Consulted:** April 17, 2012

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader Pediatric and Maternal Health Staff (Maternal Health}

Lynne Yao, MD
Acting OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Metabolic and Endocrine Products (DMEP)
Division of Risk Management (DRISK)

Drug: Lomitapide Mesylate Capsules, NDA 203858

Applicant: Aegerion Pharmaceuticals

Subject: Pregnancy Labeling

Materials Reviewed:

- Draft Lomitapide labeling submitted February 29, 2012 (with DMEP edits)
- FDA Endocrine and Metabolic Drug Advisory Committee Briefing Document (Meeting October 17, 2012)

Consult Question:
Please address the applicant's proposals for pregnancy labeling.

INTRODUCTION

On February 29, 2012, Aegerion Pharmaceuticals submitted a New Drug Application (NDA) for Lomitapide Mesylate Capsules, NDA 203858, for the indication to reduce LDL-cholesterol (LDL-C), total cholesterol (TC), apoB, and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to a low-fat diet and other lipid-lowering drugs, with or without LDL apheresis. Orphan Drug Designation was granted for this indication on October 23, 2007. The NDA was presented and discussed at an Endocrine and Metabolic Drug Advisory Committee meting held on October 17, 2012, with members voting 13 to 2 for product approval for the proposed indication.

The Division of Metabolic and Endocrine Products (DMEP) requested that the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) address the Applicant's proposals for pregnancy labeling and the proposed risk mitigation evaluation strategy (REMS) because of the suspected risk of teratogenicity based on substantive animal data. The DMEP review team, with participation by PMHS-MHT, determined that the teratogenic risk could be managed in labeling and did not require additional risk management approaches. The proposed REMS was modified to remove the inclusion of the teratogenic signal; therefore, this consult will only address recommended labeling for pregnancy, nursing mothers, and females of reproductive potential.

BACKGROUND

Lomitapide

From the October 17, 2012, FDA Endocrine and Metabolic Drug Advisory Committee Briefing Document:

> Lomitapide is an orally administered first-in-class small-molecule inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular enzyme critical to the assembly of apolipoprotein B (apoB)-containing lipoproteins in enterocytes and hepatocytes. Inhibition of MTP prevents the synthesis of chylomicrons and very-low-density lipoprotein (VLDL), which are precursors to the atherogenic low-density lipoprotein (LDL) particle. Lomitapide directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL, respectively, which ultimately give rise to the atherogenic LDL.
>
> HoFH is a life-threatening, orphan disease with an estimated prevalence of 1 in 1,000,000 in the United States. Clinical manifestations often present in childhood, with an aggressive atherosclerotic phenotype that can result in cardiovascular mortality within the first few decades of life if untreated. Although statins are the pharmacological agents of choice, individuals with HoFH have absent or dysfunctional LDL-receptors (LDL-R), which substantially attenuates the efficacy of statins. Extracorporeal removal of LDL-C (e.g., LDL apheresis) is the treatment of choice, but this therapy is not widely available, requires repeat procedures on a weekly or biweekly basis for life, and can be complicated by vascular access difficulties. Thus, there is an unmet medical need for additional LDL-lowering therapies for patients suffering from this rare disorder.

Potential Teratogenicity
Embyonic death and fetal malformations were observed in animal reproduction studies in two species when lomitapide was administered during the period of organogenesis at doses less than the human therapeutic potential. The Applicant has proposed a Pregnancy Category X in labeling for lomitapide. No human pregnancy exposure data are available for lomitapide.

Potential Tumorigencity
An increased incidence in hepatocellular tumors was seen in animal studies in mice that received lomitapide for two years. In males, these tumors were seen at clinically relevant doses and in females were seen at approximately 9-fold higher than clinically relevant doses.

DISCUSSION
Pregnancy and Nursing Mothers Labeling
The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount.

Reviewer Comment: The Applicant has proposed appropriate language and the appropriate required regulatory statement for the Nursing Mothers subsection of lomitapide labeling. The potential for tumorigenicity was seen in animal studies with mice that were dosed with lomitapide for two years at clinically relevant doses. This reviewer agrees that given the lack of information on excretion of lomitapide in human milk, along with the potential tumorigenicity signal, women should not breastfeed because of the potential exposure of children to lomitapide through human milk.

The lomitapide pregnancy subsection was restructured to comply with the current regulations, while meeting the spirit of the proposed PLLR. The review team concurred with the Applicant's proposed Pregnancy Category X classification, a contraindication for lomitapide use during pregnancy.

Reviewer Comment: This reviewer met with the DMEP review team on October 22 and 24, 2012 and discuss labeling and the pregnancy category designation for lomitapide. HoFH is a life-threatening orphan disease and the current treatment during pregnancy is repeated LDL apheresis, which is not widely available. The clinical team discussed whether lomitapide had benefit for use in pregnant women with HoFH, despite the potential for teratogenicity. If there was a potential favorable risk benefit profile for the use of lomitapide during pregnancy, then the

product should not be contraindicated during pregnancy, and a Pregnancy Category C should be considered (see Appendix A for a description of pregnancy categories). The clinical team discussed the benefit/risk of lomitapide use during pregnancy along with available therapies and decided that a Pregnancy Category X was the appropriate classification for lomitapide at this time.

As the pregnancy subsection of labeling should only address use of a drug during pregnancy, MHT proposed and provided recommendations for the addition of a subsection in Section 8.8 of lomitapide labeling, *Females of Reproductive Potential,* in order to provide information for prescribers regarding recommendations for pregnancy testing and contraception use in this population of women who are not currently pregnant, but who may become pregnant during treatment with lomitapide.

CONCLUSIONS

Labeling should adequately describe the contraindication for use of lomitapide during pregnancy, as well as conveying the potential teratogenicity information for females of reproductive potential and recommending the use of effective contraception for this population of women during lomitapide therapy. In addition, labeling should recommend against human milk-feeding in mothers taking lomitipide, due to the lack of information on excretion of lomitapide in human milk and the potential for tumorigenicity.

RECOMMENDATIONS

PMHS has the following recommendations for lomitapide Pregnancy and Females of Reproductive Potential subsections of labeling. This labeling reflects our revisions to the lomitapide labeling in the DMEP e room as of October 24, 2012.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS ----------

- Pregnancy (4, 8.1)

----------USE IN SPECIFIC POPULATIONS

- (b) (4)
-

4 CONTRAINDICATIONS

TRADENAME is contraindicated in the following conditions:

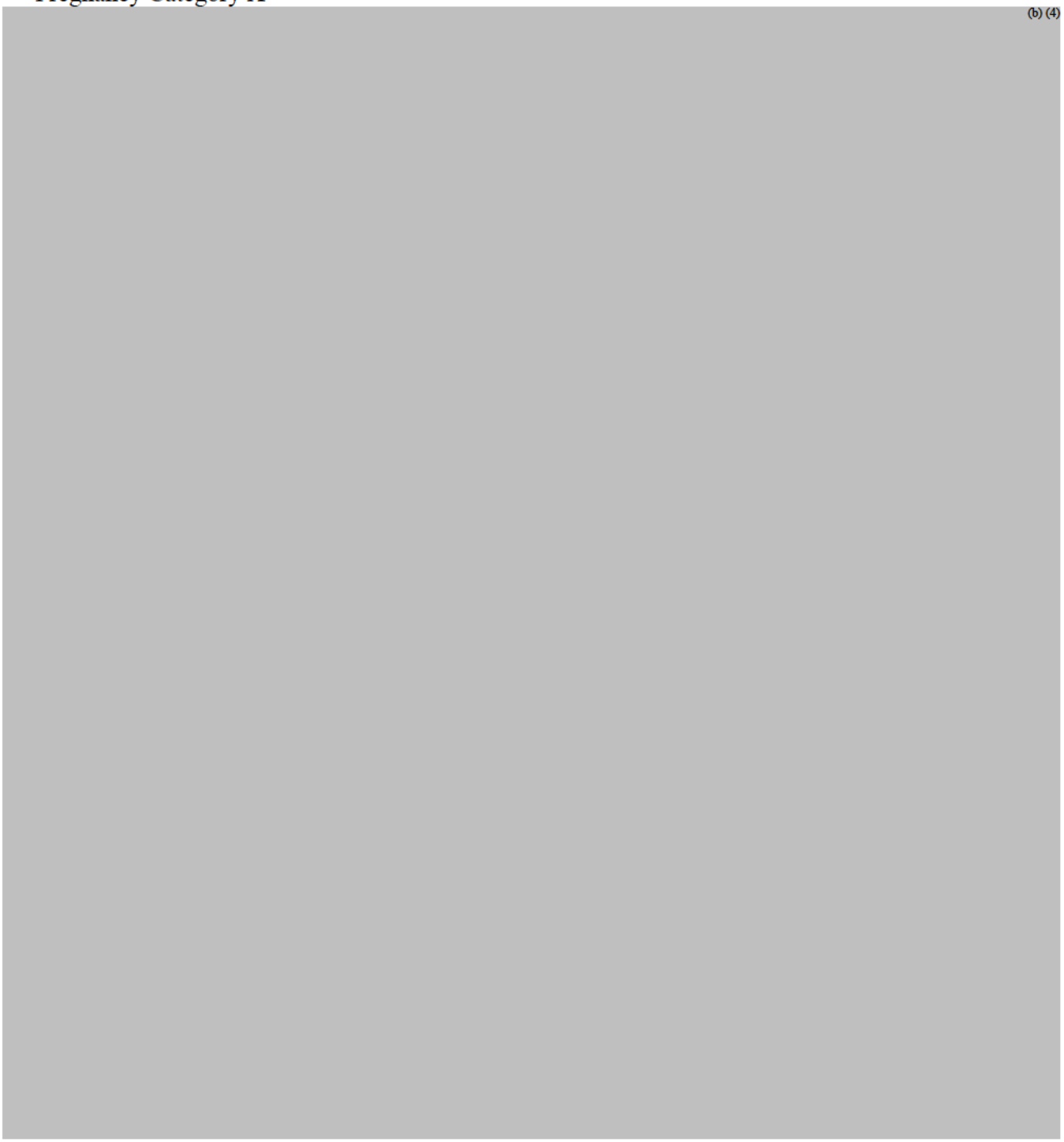
Pregnancy. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

(b) (4)



8.8 Females of Reproductive Potential

Lomitapide may cause fetal harm *[see Use in Specific Populations (8.1)]*. Females who become pregnant during Lomitapide therapy should stop Lomitapide immediately and notify their healthcare provider.

Pregnancy testing

Females of reproductive potential should have a negative pregnancy test before starting Lomitapide.

Contraception

Females of reproductive potential should use effective contraception during Lomitapide therapy**.**

Reviewer Comment: MHT recommends moving this subsection up to 8.6 to be closer to the pregnancy subsection.

17 PATIENT COUNSELING INFORMATION

- (b) (4)
- Nursing Mothers

  (b) (4)
- Females of Reproductive Potential

  Advise females of reproductive potential that they should have a negative pregnancy test before starting Lomitapide (b) (4)

APPENDIX A - FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories
(language summarized from 21 CFR 201.57)

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

JEANINE A BEST
11/06/2012

MELISSA S TASSINARI
11/06/2012

LYNNE P YAO
11/08/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Addendum to the recommendations in the review dated October 2, 2012, on Lomitapide mesylate

Date:	November 2, 2012
Reviewer(s):	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., Epidemiology Team Leader, DEPI 1, OPE, OSE
Deputy Division Director:	Tarek Hammad, M.D., Ph.D., M.Sc., M.S., Deputy Director, Division of Epidemiology 1 (DEPI1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Subject:	Addendum to the recommendations in the review dated October 2, 2012, of the Sponsor's Proposal (Version 1.0, dated February 7, 2012): "A Long-Term Prospective Observational Cohort Study (Registry) of Patients with Homozygous Familial Hypercholesterolemia Treated with Lomitapide"
Drug Name(s):	Lomitapide mesylate
Application Type/Number:	NDA 203858
Applicant/sponsor:	Aegerion Pharmaceuticals, Inc.
OSE RCM #:	2012-605
TSI #:	Not Applicable

BACKGROUND

Homozygous familial hypercholesterolemia (HoFH), an autosomal dominant disorder, results in elevated plasma levels of low-density lipoprotein cholesterol (LDL-C). Lomitapide mesylate is an MTP inhibitor indicated for patients with HoFH as an adjunct to a low-fat diet and other lipid-lowering treatments with or without LDL apheresis for the reduction of LDL-C, TC, apo B and TG. Due to the rarity of the disease, studies of lomitapide mesylate that involve a large number of participants are implausible. As a result, the sponsor proposed a product registry to better characterize the long term safety profile of lomitapide. On October 2, 2012, the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology 1 (OSE/OPE/DEPI1) recommended that this product exposure registry become a Post-Marketing Requirement (PMR) in event that the drug receives FDA approval.

In brief, this multicenter, product exposure registry of HoFH patients treated with lomitapide would enroll patients from active study sites that provide informed consent after a health care provider has decided to prescribe commercially available lomitapide. (b) (4) Data would be collected at enrollment and at usual care visits (usually at 3 month intervals). Data on all serious adverse events (including hospitalizations and emergency room visits) and AESI will be collected, sent to the sponsor and submitted for regulatory reporting as appropriate. Data will also be collected on medical procedures or medical services that the patient may receive. Special queries would be made about gastrointestinal diagnostic procedures and any new diagnosis of gastrointestinal tumors or cancers. Study outcomes include hepatic events, malignancies, pregnancy outcomes, and serum lipid levels. The proposed registry will also be used to evaluate whether prescribers adhere to the screening and monitoring information specified in the lomitapide label.

In addition to recommending that this registry be a PMR, OSE/OPE/DEPI1 also made 27 other recommendations concerning the registry that were conveyed to the sponsor on October 17, 2012. This is an addendum to those recommendations that includes one change from the previous recommendation (increasing follow-up from 8 to 10 years) and two clarifications that will elicit more details on their intended analysis. These additional recommendations to the sponsor are listed below:

ADDITIONAL RECOMMENDATIONS:

We have the following *additional* recommendations for the sponsor:

1. Increase the follow-up of all patients enrolled in the study (including patients who discontinue lomitapide) to ten years.
2. Provide fuller detail in the revised protocol (and provide mock tables) for your analyses to describe patients and lomitapide treatment including: country of treatment, age, sex, race, indications, cardiovascular history, history of apheresis and other treatments for HoFH, other medical history; lomitapide exposure, dose, duration, start date, discontinuation date, reasons for discontinuation, person-years of exposure; use of concomitant medications and start and stop dates; use of dietary

supplements; use of oral contraceptives and/or other contraceptives during lomitapide use.

3. Add Other serious adverse events to the list of outcomes for the study.

cc: BrightP/CallowayP/WysowskiD/HammadT/IyasuS/DEPI 1
EganA/JohnsonK/SmithJ/CraigE/ColmanE/ParksM/DMEP
TossaM/OSE

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/s/

PATRICIA L BRIGHT
11/02/2012

DIANE K WYSOWSKI
11/02/2012

TAREK A HAMMAD
11/04/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 30, 2012

TO: Kati Johnson, Regulatory Project Manager
James P. Smith, M.D., Clinical Reviewer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice K. Pohlman, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203858

APPLICANT: Aegerion Pharmaceuticals, Inc.
DRUG: lomitapide mesylate
NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Reduction of LDL-C, total cholesterol, apolipoprotein B, and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH)

CONSULTATION REQUEST DATE: April 12, 2012
CLINICAL INSPECTION SUMMARY DUE DATE: October 31, 2012
DIVISION ACTION GOAL DATE: December 10, 2012

PDUFA DATE: December 29, 2012

I. BACKGROUND:

Aegerion Pharmaceuticals has submitted an NDA for lomitapide mesylate, a new molecular entity proposed to treat patients with homozygous familial hypercholesterolemia (HoFH), an orphan disease. It is proposed to be used as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and triglycerides in patients with homozygous familial hypercholesterolemia. The safety and efficacy database for this population is comprised of one Phase 2 (exploratory) study (UP1001) conducted by Dr. Daniel Rader (University of Pennsylvania) and one single-arm, open-label Phase 3 pivotal study, UP1002/733-005, entitled "A Phase III Study of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor AEGR-733 in Patients with Homozygous Familial Hypercholesterolemia on Current Lipid-lowering Therapy." This protocol was inspected because the results of the study are critical to regulatory decision making.

A total of three clinical sites and the sponsor were inspected for this application. Clinical sites were chosen for inspection because the sites were among the highest enrollers in the study. The sponsor was inspected because this is a new molecular entity. These inspections are considered routine because there were no specific concerns noted during the review of the application.

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Sponsor	**Protocol #/Site # # Subjects Randomized**	**Inspection Date**	**Final Classification**
CI: Marina Cuchel, M.D., Ph.D. University of Pennsylvania 3400 Spruce Street 8039 Maloney Building Philadelphia, PA 19104	Protocol UP1002/733-005 Site # 1 5 subjects	June 25 to 27, 2012	NAI
CI: Dr. Dirk J. Blom University of Capetown Health Science Faculty, 5th Floor Chris Barnard Building, Anzio Road, Observatory Capetown, South Africa	Protocol UP1002/733-005 Site # 11 4 subjects	July 23 to 26, 2012	NAI
CI: Prof. Hendrik du Toit Theron Netcare Private Hospital, Floor 1, Room F02 Logemanstreet, Universitas Bloemfontein, South Africa	Protocol UP1002/733-005 Site #12 5 subjects	July 30 to August 2, 2012	Pending (Preliminary classification VAI)
Sponsor Aegerion Pharmaceuticals, Inc. 101 Main Street, Suite 1850 Cambridge, MA 02142	Protocol UP1002/733-005 11 sites 29 subjects	August 21 to 27, 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Marina Cuchel, M.D., Ph.D.**
University of Pennsylvania, 3400 Spruce Street
8039 Maloney Building, Philadelphia, PA 19104

a. **What was inspected**: At this site, for UP1002/733-005, six subjects were screened, five subjects were enrolled, and four subjects completed the study. An audit of all four subjects' records who completed the study was conducted.

b. **General observations/commentary:** There was no evidence of underreporting of adverse events (AEs) and the primary endpoint data were verified. No significant regulatory violations were noted and no Form FDA 483 was issued. Subject #01-002 was noted to be non-compliant, and this was reported by the CI to the sponsor who included a narrative concerning this non-compliance and adverse events in the clinical study report.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Dr. Dirk J. Blom**
University of Capetown Health Science Faculty, 5th Floor Chris Barnard Building, Anzio Road, Observatory, Capetown, South Africa

a. **What was inspected**: At this site, for UP1002/733-005, five subjects were screened, four subjects were enrolled, and four subjects completed the study. An audit of subjects' records for all five subjects who were screened for the study was conducted.

b. **General observations/commentary:** The primary endpoint data were verified. No significant regulatory violations were noted and no Form FDA 483 was issued. There was no evidence of underreporting of adverse events (AEs) by the clinical investigator to the sponsor. However, there was documentation in the source documents of adverse events for two subjects that were not in the line listings provided to the FDA field investigator. These included two adverse events (AEs) (influenza and blepharitis) at visit #14 and two concomitant medications (flustat and spevsadex) for Subject #11-004 and the AE of asthenia with concomitant medication of iron infusion for Subject #11-003 at Visit 14. These AEs and medications are documented in both the source records and CRFs and are not considered a violation by the clinical investigator. The finding

for Subject #11-004 was documented to have been reported to the FDA during the sponsor inspection and the finding for Subject #11-003 was communicated to James Smith, OND reviewer who responded that, although this AE was not in the line listings, it was included in the datasets and was thus able to be analyzed in review of the NDA.

c. **Assessment of data integrity:** The findings above are not violations by the clinical investigator. The primary efficacy data did not have any discrepancies and, for the AEs, the number of discrepancies between the line listings and the datasets is small. The datasets accurately captured the reported AEs; therefore, these findings appear to have had no significance in review of the NDA because, although not in the line listings provided to the FDA field investigator, the AEs were reported in the datasets to the NDA by the sponsor. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **Prof. Hendrik du Toit Theron**
Netcare Private Hospital, Floor 1, Room F02, Logemanstreet, Universitas Bloemfontein, South Africa

Note: Observations noted for this site are based on communications with the FDA investigator and review of a draft establishment inspection report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** At this site, for UP1002/733-005, six subjects were screened, five subjects were enrolled, and five subjects completed the study. An audit of subjects' records for all six subjects who were screened for the study was conducted.

b. **General observations/commentary:** The primary endpoint data were verified. A Form FDA 483 was issued because all the Informed Consent Forms (ICF) signed and dated by the subjects were in the Afrikaans language. These ICFs were not submitted for approval to the Independent Ethics Committee (IEC) before use. The IEC received and approved only the English language version of the ICF. There was no evidence of underreporting of adverse events (AEs) by the clinical investigator to the sponsor. However, there was documentation in the source documents of an adverse event of palpitations and hypokalemia that was not included in the line listings in the NDA. This was communicated to Dr. James Smith of the review division who noted that this AE was contained in the data listings and had been included in all analyses in the review.

c. **Assessment of data integrity:** The above findings are isolated and do not impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. **Aegerion Pharmaceuticals, Inc.**
101 Main Street, Suite 1850, Cambridge, MA 02142

a. **What was inspected:** The inspection audited Protocol UP1002/733-005 and focused on the following clinical investigators: Marina Cuchel, M.D., Ph.D., Site #1; Dr. Dirk J. Blom, Site #11; and Prof. Hendrik du Toit Theron, Site #12. Also, for review of the monitoring procedures and activities, a total of 5 study sites were chosen, one for each country plus one more, for review of monitoring reports.

b. **General observations/commentary:** The inspection reviewed the following: registration of studies on clinicaltrials.gov, selection and monitoring of clinical investigators, financial disclosures, selection of monitors, monitoring procedures and activities, quality assurance, safety and adverse event reporting, data collection and handling, and record retention. In addition, the inspection of Dr. Blom's site had noted two adverse events (AE) of influenza and blepharitis in a single subject at Visit 14 that had been reported by the clinical investigator to the sponsor but was not reported to the NDA by the sponsor. This was investigated at the sponsor site. Aegerion provided the most recent line listing in which the AE was reported. No violations were noted and no Form FDA 483 was issued.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites and the sponsor were inspected in support of this NDA. For Dr. Cuchel's site, Dr. Blom's site, and the sponsor, no violations were noted. For Dr. Theron's site, violations were noted concerning the Informed Consent Documents (ICD) because only the English version of the ICD and not the Afrikaans version were sent to the IEC for review. Also, there were 3 instances of AEs found at the clinical investigator sites that had been reported to the sponsor but were not in the line listings. These AEs were in the datasets submitted with the NDA. All of the above items are isolated findings that do not impact data integrity. The classification for Dr. Theron's site is pending and an inspection summary addendum will be generated if conclusions change upon receipt and further review of the EIR.

Based on results of these inspections it appears that data submitted by the Applicant in support of the requested indication are considered reliable.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{*See appended electronic signature pag*e}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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SUSAN LEIBENHAUT
10/31/2012

JANICE K POHLMAN
10/31/2012

SUSAN D THOMPSON
10/31/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	October 5, 2012
Reviewer:	Sarah K. Vee, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	(b) (4) (Lomitapide) Capsules, 5 mg, 10 mg, 20 mg
Application Type/Number:	NDA 203858
OSE RCM #:	2012-557

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 Introduction 1
1.1 Regulatory History 1
1.2 Product Information 1
2 Methods and Materials Reviewed 2
2.1 Labels and labeling 2
3 Conclusions 2
4 Recommendations 3
Appendices 5
Appendix A. Database Descriptions 5

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for (b) (4), NDA 203858, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

NDA 203858 for (b) (4) (Lomitapide Mesylate) Capsules was submitted to the FDA on February 29, 2012. The proprietary name review, (b) (4), is currently reviewed under a separate cover in OSE Review # 2012-1836.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 29, 2012 NDA Submission.

- Active Ingredient: Lomitapide
- Indication of Use: is a microsomal triglyceride transfer protein inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and triglycerides in patients with homozygous familial hypercholesterolemia.
- Route of Administration: oral
- Dosage Form: capsules
- Strength: 5 mg, 10 mg, 20 mg
- Dose and Frequency: The recommended starting dose is 5 mg. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg. Administered once daily at bedtime, with a glass of water and without food.
- How Supplied: Bottles of 28 capsules.
- Storage: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F); however, such exposure should be minimized. Keep container tightly closed and protect from moisture.
- Container and Closure Systems: (b) (4) HDPE bottles with child resistant closure

The Applicant proposes REMS program for this product in order to:

- Ensure that healthcare providers (HCPs) understand the appropriate use of this drug within the indicated population (patients with homozygous familial hypercholesterolemia (HoFH)).

- Minimize the serious risks of hepatotoxicity and teratogenicity that may be associated with this drug.
- Inform HCPs and patients about the serious risks associated with the use of this product.

The proposed REMS program includes the following components:

- Medication Guide
- A Dear Healthcare Provider (HCP) Letter
- A Dear Professional Society Letter
- Elements To Assure Safe Use:
  - Healthcare Providers who prescribe (b) (4) are specially certified.
  - (b) (4) will be dispensed only by a limited number of specialty pharmacy providers that agree to follow the REMS requirements.
  - (b) (4) will be dispensed only to patients with evidence or other documentation of safe-use conditions.

2 METHODS AND MATERIALS REVIEWED

We reviewed the (b) (4) container labels, carton and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 29, 2012 (Appendix B)
- Carton Labeling submitted February 29, 2012 (Appendix C)
- Insert Labeling submitted February 29, 2012 (no image)

3 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

a. Delete or minimize the graphic embedded next to the proprietary name. The graphic competes with the prominence of the proprietary and established names and product strength, which should have the most prominence on the labels and labeling.

b. Increase the prominence of the established name (which includes dosage form). Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).

c. The dosage form is part of the established name. Thus we request you to relocate "capsules: to appear following the active ingredient. For example: "(lomitapide mesylate) capsules".

d. The use of the same color font for the proprietary name, established name, and product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

- Thus, revise the color font of the 10 mg or the established name, so that the strength and the established name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths or used in the name.
- Revise the color font of the 20 mg strength or the proprietary name, so that the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

e. The gray writing on white background does not provide enough contrast and the information is difficult to read. We recommend that the color font of the writing be revised to provide greater contrast against the white background to increase readability.

f. We recommend the "Dispense the accompanying Medication Guide to each patient" statement be moved to the principle display panel. This can be achieved by minimizing the company's logo or relocating it to the side panel.

g. We recommend that the statement "28 capsules" not to be highlighted so that it does not compete with the prominence of the proprietary and established names and product strength, which should have the most prominence on the labels and labeling.

B. Insert Labeling

a. Dosage and Administration in Highlights of Prescribing Information and Full Prescribing Information:

    i. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.[2] As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:

        - Revise all instances of the symbols 'IU' to read 'international units'. The symbol 'IU' is a dangerous abbreviation because this symbol is often mistaken as IV (intravenous) or the number 10 (ten).
        - Revise all instances of the symbol '>' to read "greater than." The symbol '>' is a dangerous abbreviation that could be mistaken and used as opposite of intended.

    ii. Prior to the use of abbreviations EPA, ALA, DHA, spell out to what EPA, ALA, and DHA refer.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
10/05/2012

YELENA L MASLOV
10/05/2012

CAROL A HOLQUIST
10/05/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Sponsor's Product Registry Proposal

Date:	October 2, 2012
Reviewer(s):	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., Epidemiology Team Leader, DEPI 1, OPE, OSE
Deputy Division Director:	Tarek Hammad, M.D., Ph.D., M.Sc., M.S., Deputy Director, Division of Epidemiology 1 (DEPI1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Subject:	Review of the Sponsor's Proposal (Version 1.0, dated February 7, 2012): "A Long-Term Prospective Observational Cohort Study (Registry) of Patients with Homozygous Familial Hypercholesterolemia Treated with Lomitapide"
Drug Name(s):	Lomitapide mesylate
Application Type/Number:	NDA 203858
Applicant/sponsor:	Aegerion Pharmaceuticals, Inc.
OSE RCM #:	2012-605
TSI #:	Not Applicable

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/s/

PATRICIA L BRIGHT
10/02/2012

DIANE K WYSOWSKI
10/02/2012

TAREK A HAMMAD
10/03/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 7, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kati Johnson, DMEP

Subject: QT-IRT Consult to NDA 203858

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated July 16, 2012 regarding potential labeling revisions for NDA 203858. The QT-IRT received and reviewed the following materials:

- Your consult
- IRT QT review for NDA 203858 dated July 9, 2012
- Sponsor's proposed labeling
- Sponsor's response (dated July 13, 2012) to FDA's information request (dated July 12, 2012)

QT-IRT Comments for DMEP

QT-IRT has reviewed the TQT study for lomitapide mesylate under NDA 203858 and concluded that no significant QTc prolongation effects of lomitapide were detected, but we do not believe assay sensitivity was successfully demonstrated in the study. Even though the largest lower bound of the two-sided 90% CI for the ΔΔQTc for moxifloxacin was greater than 5 ms, the moxifloxacin profile was not consistent with expectation. Sponsor has not proposed any labeling language in the package insert.

QT-IRT has the following label recommendations which are suggestions only. We defer final labeling decisions to the review division.

12.2 ECG Effects

The effect of single doses of lomitapide on QTc interval was evaluated in a randomized, placebo- and active- controlled crossover study. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc for lomitapide was below 10 ms, the threshold for regulatory concern. However, assay sensitivity was not established in this study. Therefore, a small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out.

BACKGROUND

The sponsor conducted a thorough QT study to evaluate the potential effect of lomitapide mesylate to prolong the QTc interval. QT-IRT reviewed the study report under NDA 203858 and concluded that the study results were negative. The largest lower bound of the 2-sided 90% CI for ΔΔQTcI for moxifloxacin was greater than 5 ms at 1 h, but the rising phase of the moxifloxacin time profile was not captured. Moxifloxacin concentrations were not assessed in the study. QT-IRT therefore requested the sponsor to provide an additional time point, either at 15 minutes or 30 minutes post-dose for moxifloxacin and placebo. The sponsor replied with the following:

Per the protocol, ECGs were extracted at 1, 2, 3, 4, 5, 7, 12, and 24 hours post-dosing at which time experimental conditions were tightly controlled and standardized with subjects resting in an undisturbed environment for 15 minutes before and 5 minutes after each time point. ECGs were not extracted at either 15 minutes or 30 minutes post moxifloxacin administration and subjects were therefore not controlled in a similar manner at these time points. We do not believe that an analysis of non-pre-specified ECG time points is appropriate due to lack of strict control and standardization of subject positioning. We note that the protocol was reviewed by the FDA's IRT prior to its conduct and the ECG analysis time points were determined to be reasonable.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
08/07/2012

MONICA L FISZMAN
08/07/2012

NORMAN L STOCKBRIDGE
08/08/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE)
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY (OPE)

DATE: 24 July 2012

FROM: John R. Senior, M.D., Associate Director for Science, OPE
Leonard B. Seeff, M.D., Consultant to OPE/OSE/CDER

TO: Mary Parks, M.D., Director, Division of Metabolic and Endocrine Products (DMEP), Office of New Drugs (OND)
Amy Egan, M.D., Deputy Diector, DMEP
Eileen Craig, M.D., Medical Reviewer (mipomersin), DMEP
James Smith, M.D., Medical Reviewer r (lomitapide), DMEP

VIA: Gerald Dal Pan, M.D., Director, OSE

RCM: 2012-1005 (lomitapide)
2012-1006 (mipomersen)

SUBJECT: Possible hepatic adverse effects of lomitapide and mipomersin, new agents for treatment of elevated serum low-density lipoprotein cholesterol in patients with the orphan disease homozygous familial hypercholesterolemia (HoFH).

Documents reviewed:

1) Consultation request dated 20 April 2012 for OSE hepatology review of two new drugs, lomitapide (BMS 201038) and mipomersen (ISIS 301012), both agents associated with elevations of serum aminotransferases and induction of fatty liver

2) NDA 203858 (lomitapide) received 29 February 2012 from Aergerion Pharmaceuticals, and NDA 203568 (mipomersen) received 29 March 2012 from Genzyme Corpopation.

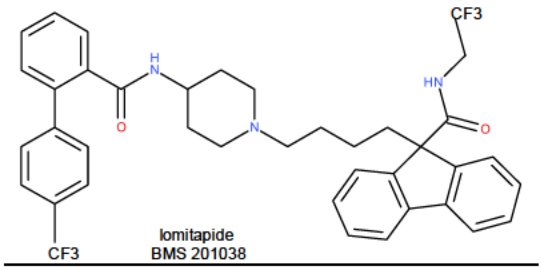
3) Selected medical literature articles on lomitapide, mipomersen, fatty liver disease, and erythropoietin for orphan indication of end-stage kidney disease requiring dialysis and repeated red blood cell transfusions.

In an earlier response dated 19 June 2012, we provided limited and only partial answers to the seven questions asked about both drugs, but focused attention on the single very serious, in fact fatal, case of death in fulminant liver failure of a 68-year-old man. He had been treated with 200 µg mipomersen weekly subcutaneous injections for six months, without notable liver injury other than modestly elevated and fluctuating serum aminotransferase elevations, but some 4.9 months after stopping it suffered catastrophic liver failure that appeared concurrent with myocardial infarction. We concluded that the case was unlikely to have been caused by a long-delayed adverse hepatic mipomersen-induced liver injury, dysfunction, and failure but much more likely

the consequence of severe and acute liver congestion and hypoxia caused by rapidly evolving acute myocardial infarction that was initially relatively silent. We did not address in detail the less serious but fairly frequent elevations of serum aminotransferase activities in other subjects treated, nor the questions posed for both drug products.

This review represents a single, formal response to the consultation request from the Division of Metabolic and Endocrine Products (DMEP) with interest in the hepatic safety of lomitapide (RCM 2012-1005) and mipomersen (RCM 2012-1006). These two new agents are being evaluated by DMEP for treatment of homozygous familial hypercholesterolemia (HoFH). HoFH is an inherited genetic disorder causes premature cholesterol deposits in arteries throughout the body and leads to a very high rate of premature death, often before reproductive age, mainly from coronary atherosclerosis. Before advent of effective lipid-lowering therapies, children and adolescents with HoFH were dying of acute myocardial infarction and had a median survival of 18 years. The worldwide incidence of this disorder is estimated at 1 per million, but in specific locales and subgroups, such as the white Afrikaners of South Africa, consanguinity has produced a much higher prevalence of about 1 per 30,000, some 30-35 times greater (Raal et al, 2011). Treating HoFH is a true orphan indication, but may provide valuable insights into the much more prevalent heterozygous form (HeFH), and other various types of hypercholesterolemia, where the future expanded market for such agents may lie. Study of the mechanism of HoFH effects led to elucidation of liver receptors for low-density lipoproteins of serum and a Nobel prize for Drs. Joseph Goldstein and Michael Brown in 1985. The two agents discussed here are quite different, but both are now under active review by the DMEP, both under suspicion of causing liver injury, at least transiently but possibly sometimes more severely.

Lomitapide has been under investigation for many years, was first discovered by Bristol-Myers Squibb as the orally administered compound BMS-201038, and now is sponsored by Aergerion Pharmaceuticals. It inhibits the microsomal triglyceride transfer protein needed for very-low-density lipoprotein (VLDL) assembly in the liver. Although it was found in a phase II trial to be probably causing elevated serum aminotransferase levels and increased liver fat in 2007, the sponsor nevertheless carried out phase III trials in 2007-2011 and has now submitted results as NDA 203858 for possible approval as treatment of HoFH.



lomitapide
BMS 201038

The other agent, **mipomersen**, is quite different, a modified 20-nucleotide antisense sequence inhibiting the messenger ribonucleic acid (mRNA) production of apo-lipoprotein B, developed originally by ISIS as 301012 and now licensed to Genzyme Corporation and further developed as

mipomersin for weekly subcutaneous injection (Kynamro®). The sponsor has submitted results for possible approval for treating homozygous familial hypercholesterolemia (NDA 203568). It also has been associated with elevated serum aminotransferase activities, and possibly with a case of fatal fulminant hepatic failure concurrent with acute myocardial infarction (see above).

(b) (4)

Rather troubling is the deception implicit in the manner in which these two agents have been investigated and the results reported for our review by the applicants, both of whom sought priority review and orphan drug status, and approval only for treatment of HoFH. The great majority of the patients and subjects studied (more than 90% for both agents), for whom data have been reported in these applications did not have HoFH, but instead a variety of disorders that cause elevated serum cholesterol levels, a vastly more common problem (and much greater potential market). From the subjects selected for study, and papers published recently, it appears obvious that the sponsors seek the larger market. It seems very likely that labeling restrictions will not be effective in limiting the use of these drugs, if approved, to patients with HoFH.

A parallel and similar situation is evident in the story of erythropoietin development for treating severe anemia in patients with renal failure requiring long-term, recurrent dialysis and repeated transfusions. Orphan disease status was granted in 1984, based on a prevalence of about 50,000 cases in the United States at that time. I had consulted to the Office of Orphan Drug Products 1984-1994 as an outside consultant before becoming employed at CDER in 1995, evaluating the data submitted by Chugai-Genetics Institute about 1986 for OOPD and recommending approval of their product MAROGEN about 1988 or so. But recombinant erythropoietin (epoetin alfa), as a competing Amgen product (given trade names EPOGEN and PROCRIT) was approved for the orphan indication in 1989 with seven-year exclusivity, and Chugai lost in a patent dispute. The indication was expanded in 1993 by Amgen to anemia in cancer patients on chemotherapy and HIV-infected patients on ziduvodine, and several times since. Although the OODP awarded orphan product grants to the developer to gather data on dialysis patients, expanded indications soon made the drug a non-orphan and the market exploded to billions of dollars annually, as described in the Washington Post front-page article by Peter Whoriskey (on Friday 20 July 2012). The effect of granting exclusivity to one orphan product and excluding competitors should be noted, especially when the "orphan" evolves into a blockbuster.

In preparation for the meeting later this week of the Risk Evaluation Management Strategy Oversight Committee, we submit these opinions now. The questions asked about both of these quite dissimilar these agents, both proposed for treatment of HoFH, were:

> *1) Are the available data adequate to assess hepatic safety and potential monitoring mechanisms for these drug products in the HoFH population?*
> *2) Do the hepatic biomarkers (e.g., CK18 and its fragments, ELF panel) performed by the sponsor provide any clinically useful information?*

3) Are the labeled recommendations from the sponsor adequate to assess and monitor liver safety if these drugs were to be approved?
4) Are there subgroups of particular interest (e.g., demographic or baseline characteristics) that we should ensure we study with interest during the review with regard to liver safety?
5) Please provide recommendations for several GI/hepatologists who can sit on the AC panel.
6) Should these products be approved, what monitoring (enhanced pharmacovigilance, registry, etc.) would you propose to further assess liver safety post-approval?
7) Are there additional concerns unique to the pediatric population that would necessitate different monitoring of liver safety in pre-approval trials?

Although the two agents are quite different in structure, mechanism of actions, and other ways, the questions are generic and can be responded to, at least provisionally as follows:

1) Are the available data adequate to assess hepatic safety and potential monitoring mechanisms for these drug products in the HoFH population?

In general, there are two problems that are unresolved: 1) the rather frequent incidence of serum aminotransferase elevations, albeit without much in functional disturbance as indicated by serum bilirubin and prothrombin times; and 2) the frequent induction of fatty liver in many or most of the patients receiving these drugs.

1) In review of transaminase elevations in patients with homozygous hypercholesterolemia, there do not appear yet to be any with elevated serum bilirubin or jaundice that are clearly or probably drug induced. However, it had been observed almost two decades ago by Bob Temple that when a drug causes more frequent serum aminotransferase elevations than placebo or control agents, then it may (but not always) be suspected that rarer but more serious cases of liver injury with dysfunction may occur, and should be looked for very carefully. One serious, fatal case of fulminant liver failure, in the man five months after stopping mipomersen, was assessed in the earlier consultation of 19 June, and we judged it to be probably caused by evolving fatal myocardial infarction. We have not assessed the larger database of patients with other types of serum cholesterol elevation submitted along with the modest numbers with HoFH, for which evaluation for approval was not requested.

2) The other question of how to interpret and evaluate the fatty livers seen in so many of the patients receiving these drugs is even more difficult. Despite hundreds of recent papers published about fatty liver disease and its more threatening variant of steatohepatitis that may progress slowly to cirrhosis and carcinoma in some, it is still not known how to tell which persons will progress and which will not. Newer biomarkers of CK18 and others are of research interest, but not yet reliable clinical tools to help us. Clearly we shall have to observe treated patients longer to find out. We have no sure way to distinguish benign non-progressive fatty liver from steatohepatitis with chronic low-grade inflammation that will become worse. At present only liver biopsy can be relied upon to make distinctions. If new drugs are causing both fatty liver and aminotransferase elevations, the problem is even more challenging.

The question of monitoring to detect and act upon possible evidences of liver injury, both during clinical trials but more of concern, after marketing, raises many issues about whether monitoring as usually specified in labeling accomplishes anything useful at all, even if done as advised, and experience has shown unfortunately that it is rarely done at all for very long. In short, the data available are not sufficient to provide assurance that routine monitoring serum aminotransferase activities will protect patients from possible serious liver injury beyond the apparently benign and reversible elevations observed so far. For life-shortening HoFH, long-term treatment with continued observation of liver tests is perhaps reasonable, if it is required to be done, but we are far from ready to advise extending use of these agents to life-time treatment of diverse forms of hypercholesterolemia that is less imminently threatening. If these agents are inducing simple fatty liver that does not ever progress to active steatohepatitis, there would be less concern. We do not know that yet. The combination of frequent induction of fatty liver and elevated serum aminotransferase activities is worrisome.

2) Do the hepatic biomarkers (e.g., CK18 and its fragments, ELF panel) performed by the sponsor provide any clinically useful information?

These are interesting biomarkers whose value has not yet been proved. Detection of hepatic fibrosis without liver biopsy is a research question yet to be answered. We do know that it usually takes years or even decades for progression of steatohepatitis to cirrhosis, and that imaging methods are not sensitive for detecting stages along the way. For relatively short-term studies, as submitted in these NDAs, we are more concerned about induction of acute liver injury in some people, although serious effects might be uncommon. We do not yet know whether these agents are causing heparin-like elevations of serum aminotransferases that do not progress to serious liver dysfunction, or not. Simple levels or grades of elevation of enzyme activities, as proposed and used by the National Cancer Institute, do not really serve as measures of liver dysfunction or clinical severity. The most recent comprehensive review of fatty liver disease not caused by alcohol consumption cites a simple model for likelihood of steatohepatitis (NASH) in those with fatty liver, using serum alanine aminonotransferase (ALT) and fasting insulin (FI), (Torres et, 2012) . In that model, the sensitivity and specificity for detecting NASH in people with fatty liver in which prevalence of NASH was 0.30 were both 75% (area-under-receiver-operating characteristic, 0.81), using a cut-off value of -0.806: probability of NASH = ALT x 0.042 + FI x 0.095 – 4.246.

3) Are the labeled recommendations from the sponsor adequate to assess and monitor liver safety if these drugs were to be approved?

The labeling submitted with the two NDAs shows some variance between the two drugs, and it seems preferable that both be the same, since both are for exactly the same indication. No reason has been established for allowing different labeling and different interpretations. Both drugs appear to cause both fatty liver and elevated serum aminotransferase activities, and so justify the same monitoring methods and frequency, and the same responses to abnormalities detected. Even after one or both of these drugs is approved for treating HoFH (only), we still have much to learn about their long-term effects. Therefore it seems reasonable to require the labeling to state

clearly how the diagnosis of HoFH is to be established. The different draft labeling proposed in the initial NDA submissions at end-February (lomitapide) and (b) (4) (mipomersen) should be made the same, so that all possible additional information can be gathered. The frequency of monitoring, what should be monitored, and what should be done about abnormalities should be standardized, and not left to the vagaries of various treating physicians.

We feel that pretreatment measures of serum alanine and aspartate aminotransferase activities (ALT and AST), alkaline phosphatase activity (ALP), total serum bilirubin concentration (TBL) be done at least twice biweekly, and that on-treatment monthly monitoring of tests be done for a year. If modest elevations of ALT (>3 to 5xULN) are found, the tests should be repeated within a week, preferably at a local laboratory so that results will be immediately available to the treating physician. If ALT >5 to 10xULN, repeat tests within 4 days; and if >10x, within 2 days and treatment interrupted for clinical investigation to determine the probable cause. If none is found, then rechallenge with the drug should be done cautiously, with twice weekly measures of the liver tests. Measuring prothrombin time may also be a useful test of a liver function.

4) Are there subgroups of particular interest (e.g., demographic or baseline characteristics) that we should ensure we study with interest during the review with regard to liver safety?

Because of the extreme rarity of HoFH, it is most unlikely that large numbers of subjects will be available at any location, or even in an entire trial population, sufficient to divide them into subgroups, so this approach is probably not going to be of substantial value. The stratagem of recruiting additional subjects with the more common but less threatening heterozygous form of familial hypercholesterolemia (HeFH) instead does not really address what is being studied and requested here. However, sub-grouping for study of HeFH will make very good sense, for a later submission in the future.

5) Please provide recommendations for several GI/hepatologists who can sit on the AC panel.

Dr. Seeff has recommended (b) (4) as hepatologist, (b) (4) as hepatopathologist, and (b) (4) as pediatric hepatologist. Dr. Senior adds that perhaps (b) (4) might be considered as alternate hepatologists. Some of these may already be asked to serve as consultants to the sponsors, and not available to us. If the list is restricted to those who are special government employees, fewer choices are available.

6) Should these products be approved, what monitoring (enhanced pharmacovigilance, registry, etc.) would you propose to further assess liver safety post-approval?

Because efforts at vigilance and monitoring have not been very successful to date, despite vast expenditures of effort and cost, this whole issue needs to be carefully reconsidered. The situation is particularly bad after approval and marketing of new drugs, expansion of the population of patients treated without the rigor imposed during clinical trials of selected subjects. In the "real

world" of post-approval pharmacovigilance, there is dependence on the ability and willingness of physicians to report cases with sufficient detail to enable evaluation of the true severity and likely causes of liver test abnormalities; many physicians never report cases at all, and even those that are reported to sponsoring companies lack necessary information to make a diagnosis of probable cause. Even the monitoring of controlled clinical trials could be improved, but the issue involved will require careful and extensive discussions with the many parties that are concerned and involved.

7) *Are there additional concerns unique to the pediatric population that would necessitate different monitoring of liver safety in pre-approval trials?*

If this study is directed at HoFH, as advertised, then a sizeable proportion of them are pediatric, for many of those afflicted with this dire disorder did not reached full adulthood, in the days before lipid-lowering drug treatment was available. The onset of the disorder begins in infancy and early childhood, when effective treatment might be most valuable in preventing progressive atherosclerosis. There definitely should be pediatric trials conducted, as a condition for approval, and completed within a reasonable time for review and evaluation. This question is an indication that the sponsors really want to study heterozygous familial hypercholesteremia (HeFH), ans well as other forms of adult hypercholesterolemia, considerably more common conditions.

In summary, we have many concerns and few answers. We are pushing limits of what is known, and see the treatment of patients with HoFH as an opportunity to learn more about the long term effects of cholesterol lowering despite initiation of fatty liver and causation of possibly non-serious forms of hypretransaminasemia, if no serious cases of hepatotoxicity occur. For most drugs, concern regarding possible adverse effects on the liver focuses on possible development of acute liver injury. This concern holds also for both lomitapide and mipomersen, in view of the frequent occurrence of raised levels of aminotransferases, but there is the second concern of the possible development of chronic liver disease because of the equally common development of fatty liver disease. Little is known about the consequences of drug-induced fatty liver disease, whether it manifests as or progresses to the more serious form of simple fatty liver disease, namely non-alcoholic steatohepatitis (NASH) that may progress over decades to advanced chronic liver disease, cirrhosis and even the development of hepatocellular carcinoma. This is particularly relevant concern since these drugs will presumably be administered to those with HoFH for the rest of their lives. It is therefore imperative that long-term evaluation be performed to address this concern that would include regular screening for evidence of liver dysfunction. Over time, evaluation may need to include performing liver biopsies to fully determine whether there is incipient or even established steatohepatitis that would require consideration of whether or not to continue treatment with one or other drug

There does not seem to be great urgency to approve life-saving drugs for patients in immediate danger. The disease itself, HoFH, although formerly fatal to those affected before the age of child-bearing, in more recent years has shown that death can be delayed considerably by lipid-lowering treatment, so that some patients are surviving into their fifth or sixth decades. We should not repeat the mistakes of the past by allowing approval for an orphan problem to be used to persuade physicians into much more widespread use before we understand the problems we may be causing.

John R. Senior, M.D. Leonard B. Seeff, M.D.

cc: OSE 2012-1006
M. Parks, DMEP
A. Egan, DMEP
E. Craig, DMEP
L. Seeff, OSE/OPE
G. Del Pan, OSE/OPE

REFERENCES

Homozygous Familial Hypercholesterolemia

Goldstein JL, Brown MS. Familial hypercholesterolemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. Proc Natl Acad Sci USA. 1973 Oct;70(10):2804-8.

Brown MS, Goldstein JL. Michael S. Brown, MD and Joseph L. Goldstein MD. 1985 Nobel laureates in medicine. J Invest Med. 1996 Feb;44(2):14-23.

Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. J Clin Invest. 2003 Jun;111(12):1798-803.

Raal FJ, Pilcher GJ, Panz VR, vanDeventer HE, Brice BC, Blom DJ, Marais AD. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011 Nov 15;123(20):2202-7.

Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 2012 Feb;16 (Epub ahead of print).

Lomitapide

Robl JA, Sulsky R, Sun CQ, Simpkins LM, Wang T, Dickson JK, Chen Y, Magnin DR, Taunk P, Slusarchuk WA, Biller SA, Lan SJ, Connolly F, Kunselman LK, Sabrah T, Jamil H, Gordon D, Harrity TW, Wetterau JR. A novel series of highly potent benzimidazole-based microsomal triglyceride transfer protein inhibitors. J Med Chem. 2001 Mar 15;44(6):851-6.

Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, Millar JS, Ikewaki K, Siegelman ES, Gregg RE, Rader DJ. Inhibition of microsomal triglyceride transfer protein in falilial homozygous hypercholesterolemia. N Engl J Med. 2007 Jan 11;356(2):158-56.

Rizzo M. Lomitapide, a microsomal triglyceride transfer protein inhibitor for the treatment of hypercholesterolemia. IDrugs 2010 Feb;13(2):103-11.

[No authors listed] Lomitapide. Am J Cardiovasc Drygs. 2011 Oct 1;11(5):347-52.

Mipomersin

Kastelein JJP, Wedel MK, Baker BF, Su J, Bradley JD, Yu RZ, Chuang E, Graham MJ, Crooke RM. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation2006 Oct 17; 114(16):1729-35. Epub 2008 Oct 9.

Ito MK. ISIS 301012 gene therapy for hypercholesterolemia: sense,antisense, or nonsense? Ann Pharmacother. 2007 Oct;41(10):1669-78.

Raal FJ, Santos RD, Blom DJ, Mipomersin, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with with homozygous familial hypercholesterolemia; a randomized, double-blind; placebo-controlled trial. Lancet 2010; 375:998-1006.

Ricotta DN, Fisjman W. Mipomersin: a safe and effective antisense therapy adjunct to statins in patienrts with hypercholesterolemia. Cadiol Rev. 2012 Mar-Apr; 20(2):80-5.

Furtado JD, Wedel Mk, Sacks FM. Antisense inhibition of apoB synthesis with mipomersin reduces plasma apoC-III and apoC-III-containing lipoproteins. J Lipd Res. 2012 Apr;54(4):784-91.

Visser ME, Wagener G, Baker BF, Geary RS, Donovan M, Beuers UH, Nederveen AJ, Verheij J, Trip MD, Basart DC, Kastelein JJ, Stroes ES. Mipomersin, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind; placebo-controlled trial. Eur Heart J. 2012 May;33(9):1142-9.

Parhofer FG. Mipomersin: evidence-based review of its potential in the treatmnent of homozygous and severe heterozygous familial hypercholesterolemia. Core Evid. 2012;7:29-38. Epub 2012 May 31.

Visser ME, Witztum JL, Stroes ES, Kastelein JJ. Antisense oligonucleotides for the treatment of hypercholesterolemia. Eur Heart J. 2012 June;33(12):1451-8.

Geisinger C, Steinhagen-Theissen E, Kassner U. Therapeutic potential of mipomersin in the management of familial hypercholesterolemia. Drugs 2012 Jul 16; Epub ahead of print.

Fatty Liver-Steatohepatitis

Cheung O, Sanyal AJ. Recent advances in nonalcoholic fatty liver disease. Curr Opin Gastroenterol. 2010 May;26(3):202-8.

Vernon G, Baranova A, Younossi ZM. Systemic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2011 Aug;34(3):274-85.

Torres D, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2012 Aug;10(8):837-58. Epub 20122 Mar 23.

Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Semin Liver Dis.2012 Feb;32(1):2-13. Epub 2012 Mar 13.

Ahmed A, Keeffe EB. Asymptomatic elevation of aminotransferase levels and fatty liver secondary to heterozygous hypobetalipoproteinemia. Am J Gastroenterol. 1998 Dec;93(12): 2598-9.

Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice guidelines by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005-2022

Erythopoietin

Whoriskey P. Dangerous doses, big profits. Washington Post Friday 20 July 2012:A1, A6-A7.

Goldwasser E. Erythropoietin: a somewhat personal history. Perspect Biol Med. 1996 Autumn; 40(1):18-32/

Erslev A. The discovery of erythropoietin. ASAIO J. 1993 Apr-Jun;39(2):89-92.

Gershon D. Biotechnology patents. Amgen scores a knockout. Nature 1991 Mar 14; 350(6314):99.

Miyake T, Kung CHK, Goldwasser E. The purification of erythropoietin. J Biol Chem. 1977 Aug 19;252(15):5558-64.

Jacobson L, Goldwasser E, Fried W, Plzak LF. Studies on erythropoiesis. VII. The role of the kidney in the production of erythrocytes. Trans Assoc Am Physicians. 1957;70:305-17.

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/s/

MARGARITA V TOSSA
09/13/2012

ALLEN D BRINKER
09/13/2012

EXECUTIVE CAC MINUTES

Date of Meeting: 24 July 2012

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
David Jacobson Kram, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DTOP, Alternate Member
Karen Davis-Bruno, DMEP, Pharm Tox Supervisor
Tim Hummer, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: Tim Hummer

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND/NDA#: 50,820 / 203,858
Drug Name: AEGR-733 (lomitapide)
Sponsor: Aegerion Pharmaceuticals

Background:
AEGR-733 is a microsomal triglyceride transfer protein (MTP) inhibitor being developed for the treatment of hypercholesterolemia in patients with homozygous familial hypercholesterolemia, which is an orphan population. The NDA currently under review is only for the orphan population; the sponsor intends for the mouse carcinogenicity study to be the primary study to support marketing approval. A rat study is included as supportive information.

Mouse Carcinogenicity Study:
The sponsor conducted a 2-year bioassay in CD-1 mice. Mice (60/sex/group) were administered AEGR-733 by oral administration (mixed in diet) at dose levels of 0 (diet control), 0.3, 1.5, 7.5, 15 or 45 mg/kg/day. Because of survival issues, once a group size reached 20 animals, dosing was stopped for that particular group for the remainder of the study. This resulted in male groups being left untreated for 2 to 14 weeks at the end of the study and female groups being left untreated for 0 to 8 weeks at the end of the study. Additionally, because of mortality issues, the male high-dose group was sacrificed at the end of Week 98, the male mid-dose group was sacrificed at the end of Week 101, and the remaining male groups were sacrificed at the end of Week 104. All female groups were sacrificed at the end of Week 99.

Because AEGR-733 inhibits absorption of fat soluble vitamins from the intestine that can lead to toxicity due to vitamin deficiency, all animals were fed a rodent diet that contained more vitamin A and K than standard rodent diet. Additional vitamin

supplementation was not employed.

A statistically significant increase in the incidence of hepatocellular neoplasms (adenomas or carcinomas, combined) was observed in males given ≥1.5 mg/kg/day and females given ≥7.5. Both hepatocellular adenomas and carcinomas occurred singly or in multiples and several animals had both adenomas and carcinomas. Statistically significant increases in adenomas or carcinomas, combined, of the small intestine (duodenum, ileum, and jejunum) were observed in males and females at ≥15 mg/kg/day. The jejunum was the most common site for carcinomas. The incidences of hepatocellular and small intestinal neoplasms was not completely dose dependent, as there were often fewer neoplasms at the high dose compared with lower dose levels; this effect was likely due to the higher mortality rate in the high-dose groups.

The NOEL for drug-related neoplasms in mice was 0.3 mg/kg/day for males and 1.5 mg/kg/day for females based on the statistical significance of hepatocellular neoplasms at ≥1.5 mg/kg/day for males and ≥7.5 mg/kg/day for females, which represent clinical exposure margins of 2X and 9X, respectively. A summary of neoplasm incidence, statistical significance, and clinical exposure margins for parent compound and its major metabolites are shown in the tables below.

Neoplastic Findings in Male Mice

	Males					
Dose (mg/kg/d)	0	0.3	1.5	7.5	15	45
No. Examined	60	60	60	60	60	60
Exposure Margin[†]						
AEGR-733	NA	0.4X	2X	11X	26X	77X
Metabolite M1	NA	NC	14X	115X	300X	1600X
Metabolite M3	NA	0.2X	0.8X	4.6X	11X	34X
Liver						
Hepatocellular adenoma	**4*** (0.0011)	5	13	11	**16*** (0.0034)	**15*** (0.0013)
Hepatocellular carcinoma	23	22	**40*** (0.0088)	**38*** (0.0076)	36	30
Both adenoma and carcinoma	2	2	9	7	9	8
Total with hepato-cellular tumors	25 (0.0131)	25	**44*** (0.0061)	**42*** (0.0024)	**43*** (0.0071)	37 (0.0103)
Duodenum						
Adenoma	0	2	0	0	0	0
Carcinoma	**0*** (0.0107)	0	0	0	2 (0.2534)	2 (0.1875)
Total with duodenal tumor	0	2	0	0	2	2
Jejunum						
Adenoma	0	0	0	1	0	0
Carcinoma	**0*** (0.0110)	0	1	1	**6*** (0.0149)	3 (0.0786)
Total with jejunal tumor	0	0	1	2	**6*** (0.0149)	3 (0.0786)
Ileum						
Adenoma	0	0	0	0	0	0
Carcinoma	0	0	0	0	1	0
Total with ileal tumor	0	0	0	0	1	0
Small Intestine Combined (duodenum + jejunum + ileum)						
Adenoma	0	2	0	1	0	0
Carcinoma	**0*** (<0.001)	0	1	1	**9*** (0.0019)	**5*** (0.0144)
Total with small intestinal tumor	**0*** (0.0039)	2	1	2	**9*** (0.0019)	**5*** (0.0144)

[†]Based on $AUC_{0\text{-}24}$ (ng·h/mL); mean human exposures at 60 mg/day for parent, M1, and M3 are 69.5, 6.5, and 535 ng·h/mL, respectively.
For Trend analysis: *p≤0.005 for common tumors and p≤0.025 for rare tumors.
For Pair-wise comparisons: *p≤0.01 for common tumors and p≤0.05 for rare tumors.
NA = not applicable; NC = not calculated (plasma concentration below the limit of quantitation).

Neoplastic Findings in Female Mice

	Females					
Dose (mg/kg/d)	0	0.3	1.5	7.5	15	45
No. Examined	60	60	60	60	60	60
Exposure Margin†						
AEGR-733	NA	0.4X	2X	9X	22X	77X
Metabolite M1	NA	NC	14X	86X	290X	1025X
Metabolite M3	NA	0.1X	0.4X	2.5X	8X	20X
Liver						
Hepatocellular adenoma	**1*** (<0.001)	0	1	**12*** (0.0035)	**12*** (0.0051)	**10*** (0.0065)
Hepatocellular carcinoma	**4*** (0.0016)	0	1	**17*** (0.0049)	16 (0.0119)	11
Both adenoma and carcinoma	0	0	0	6	3	2
Total with hepato-cellular tumors	**5*** (<0.001)	0	2	**23*** (<0.001)	**25*** (<0.001)	**19*** (0.0025)
Duodenum						
Adenoma	0	0	0	0	2	0
Carcinoma	0	0	0	0	0	1
Total with duodenal tumor	0	0	0	0	2	1
Jejunum						
Adenoma	0	0	0	0	2	0
Carcinoma	0	0	0	0	5 (0.0542)	1
Total with jejunal tumor	0	0	0	0	7	1
Ileum						
Adenoma	0	0	0	0	0	0
Carcinoma	0	0	0	0	0	1
Total with ileal tumor	0	0	0	0	0	1
Small Intestine Combined (duodenum + jejunum + ileum)						
Adenoma	0	0	0	0	3	0
Carcinoma	**0*** (0.0086)	0	0	0	5 (0.0542)	3 (0.1304)
Total with small intestinal tumor	**0*** (0.0111)	0	0	0	**8*** (0.0083)	3 (0.1304)

†Based on $AUC_{0\text{-}24}$ (ng·h/mL); mean human exposures at 60 mg/day for parent, M1, and M3 are 69.5, 6.5, and 535 ng·h/mL, respectively.
For Trend analysis: *p≤0.005 for common tumors and p≤0.025 for rare tumors.
For Pair-wise comparisons: *p≤0.01 for common tumors and p≤0.05 for rare tumors.
NA = not applicable; NC = not calculated (plasma concentration below the limit of quantitation).

Rat Carcinogenicity Study:
The sponsor conducted a 2-year bioassay in Sprague-Dawley rats. Rats (60/sex/group) were administered AEGR-733 once daily by oral gavage at dose levels of 0 (vehicle), 0.25, 1.7, or 7.5 mg/kg/day in males or 0 (vehicle), 0.03, 0.35, or 2.0 mg/kg/day in females. Females received lower dose levels because females had a greater drug exposure than males at equivalent doses. The female group receiving 0.03 mg/kg/day was euthanized during Week 94 and all remaining female groups were sacrificed during Week 97. All male groups were euthanized during Week 98. The vehicle was 75% PEG-400; a second control group receiving water was not utilized in this study.

Because AEGR-733 inhibits absorption of fat soluble vitamins from the intestine that can result in toxicity due to vitamin deficiency, all animals were fed a rodent diet that contains more vitamin A and K than standard rodent diet. Beginning on Day 407, all animals in the mid-dose group received a vitamin-fortified diet containing 5 times the concentrations of vitamins A, D, and E contained in the standard diet and all animals in the high-dose group received a vitamin-fortified diet containing 10 times the concentrations of vitamins A, D, and E. The decision regarding when to supplement the diet with additional vitamins was dependent upon the measurement of vitamins in blood and liver from another group of animals that were being treated concurrently with the same dose levels, but conducted and reported under a different study number.

There were no drug-related increases in neoplasms at any dose tested. Therefore, the NOEL for drug-related neoplasms in rats was considered to be the highest dose tested: 7.5 mg/kg/day for males and 2 mg/kg/day for females. At the male NOEL, respective exposures for the parent, M1 metabolite, and M3 metabolite are approximately 6, 13, and 1 times the anticipated clinical exposures at 60 mg/day. At the female NOEL, respective exposures for the parent, M1 metabolite, and M3 metabolite are approximately 8, 8, and 3 times the anticipated clinical exposures at 60 mg/day.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee found the study to be acceptable despite the high mortality.
- The Committee concurred that the following neoplasms were drug related:
    - Incidence of animals with hepatocellular adenomas, carcinomas, and combined adenomas or carcinomas in males at ≥1.5 mg/kg/day and females at ≥7.5 mg/kg/day.
    - Combined incidence of animals with adenomas or carcinomas in the small intestine of males and females at ≥15 mg/kg/day.

Rat:

- The Committee considered the study to be acceptable, although suboptimal. The vehicle may have affected incidences of pancreatic acinar neoplasms.

- The Committee concurred that there were no drug-related neoplasms.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DMEP
/KDavisBruno, DMEP
/THummer, DMEP
/KJohnson, DMEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
08/01/2012

ABIGAIL C JACOBS
08/01/2012

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA/IND	203858
Brand Name	Not determined
Generic Name	Lomitapide mesylate
Sponsor	Aegerion Pharmaceuticals, Inc.
Indication	Homozygous familial hypercholesterolemia (HoFH)
Dosage Form	Oral capsules (5, 10 and 20 mg)
Drug Class	Inhibitor of microsomal triglyceride transfer protein (MTP)
Therapeutic Dosing Regimen	Recommended starting dose of 5 mg. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg. To be taken once daily at bedtime.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Stepwise escalation (5 mg x 2 wks, 10 mg x 4 wks, 20 mg x 4 wks, 40 mg x 4 wks, 60 mg) to individualized MTD or a maximum dose of 60 mg.
Submission Number and Date	SDN 001 / 29 Feb 2012
Review Division	DMEP

Note: Any text in the review with the light background should be inferred as copied from the sponsor's documentation

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of lomitapide (75 and 200 mg doses sequentially) and 75 mg lomitapide co-administered with ketoconazole were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between lomitapide (75 and 200 mg) and placebo, and between 75 mg lomitapide co-administered with ketoconazole and ketoconazole were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms; however, the rising phase for moxifloxacin is missing based on the moxifloxacin time profile (Figure 3). We would like to evaluate one more time point, either at 15 minutes or 30 minutes after moxifloxacin was administered.

In this phase 1, randomized, single-center, 6-treatment, 5-period, crossover study, 56 healthy subjects received 75 mg lomitapide, 200 mg lomitapide, 75 mg lomitapide co-administered with ketoconazole, placebo, ketoconazole 200 mg, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs for 75 mg Lomitapide, 200 mg Lomitapide, 75 mg Lomitapide + Ketoconazole, Moxifloxacin and Ketoconazole (FDA Analysis)

Treatment	Time (h)	ΔΔQTcI (ms)	90% CI (ms)
75 mg Lomitapide	**24**	**1.1**	**(-0.8. 3.1)**
200 mg Lomitapide	12	2.8	(0.3, 5.4)
75 mg Lomitapide + Ketoconazole*	24	2.7	(0.2, 5.3)
Moxifloxacin 400 mg**	1	12.5	(9.8, 15.2)
Ketoconazole	3	6.4	(3.7, 9.2)

* Ketoconazole-corrected change from baseline in QTcI.

** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.8 ms.

The therapeutic dose of 75 mg lomitapide administered orally as a solution was selected based on the PK characteristics of lomitapide. The predicted C_{max} for a 75-mg solution dose is 8 to 9 ng/mL, which is approximately the steady state C_{max} following 50-mg multiple oral capsule dosing (8.5 ng/mL).

To address the investigation of the expected high clinical exposure scenario, the sponsor reports the supratherapeutic dose of lomitapide (75 mg solution co-administered with ketoconazole at a fed state) was selected to mimic the exposure that could occur in the target population in the worst circumstances (e.g., concomitant liver disease, taking more than the clinical dose prescribed, concomitant use with an inhibitor of CYP 3A4). This high clinical exposure regimen (75 mg solution co-administered with ketoconazole at a fed state) results in a mean lomitapide C_{max} and AUC that are about 23- and 6-fold the expected mean C_{max} and AUC for a 60 mg q.d. dose at fasting steady state, respectively. The single 200-mg solution dose (supratherapeutic) of lomitapide results in a mean C_{max} and AUC that are about 16- and 4-fold, respectively, the expected mean C_{max} and AUC for a 60-mg q.d. dose at steady state. The proposed label states concomitant administration of lomitapide with moderate or strong CYP3A4 inhibitors (e.g., ketoconazole) is contraindicated, which would mitigate the concerns about 23-fold higher C_{max}.

The other high exposure clinical exposure is considered to occur in patients with moderate to severe hepatic failure where increases in C_{max} of ~361% were seen compared to healthy controls. Again, for patients with moderate or severe hepatic impairment, lomitapide is contraindicated, in view of the potential effect of the drug on the liver. Mild hepatic impairment increased lomitapide C_{max} exposures only 4% (not clinically relevant). With regard to renal impairment, a modest increase in C_{max} (4%) was observed and is not considered clinically significant. This increase would be mitigated by the individualized dose escalation regimen proposed for use in the clinical setting.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

Sponsor did not propose any labeling language in the package insert.

2.2 QT-IRT Recommended Label

QT-IRT will provide recommendations for the labeling after reviewing ECGs for moxifloxacin at 15 minutes or 30 minutes post-dose.

3 BACKGROUND

3.1 Product Information

AEGR-733 (formerly known as BMS-201038 or BMS-201038-04 and referred to as lomitapide throughout this document) is a selective inhibitor of MTP. Inhibition of MTP prevents the assembly of apoB-containing lipoproteins in hepatocytes and enterocytes and limits the release of these lipoproteins into the systemic circulation.

3.2 Market approval status

Lomitapide is not approved for marketing in any country.

3.3 Preclinical Information

From eCTD 2.6.2

Lomitapide (also Known as AEGR-733 and BMS-201038), BMS-203215, and BMS-203304: Effects on hERG Tail Current Recorded from Stably Transfected HEK293 Cells.

The purpose of this GLP study was to evaluate lomitapide and its primary metabolites M1 and M3 for in vitro effects on the hERG channel current (IKr, the rapidly activating delayed rectifier cardiac potassium current). Lomitapide was tested at free-base concentrations of up to 3 µM (approximately 2100 ng/mL). M1 and M3 were tested at concentrations up to 300 µM (approximately 105 and 113 µg/mL, respectively). Lomitapide had an IC50 value for hERG inhibition of 1.7 µM (approximately 1200 ng/mL, which is approximately 220× the estimated Cmax in humans at 60 mg). The M1 metabolite had an IC50 value of 135 µM and the M3 metabolite had an IC50 value of >300 µM.

3.4 Previous Clinical Experience

From eCTD 2.7.4.

Electrocardiograms: HoFH Study Pool

In Study UP1002/AEGR-733-005, the Applicant enlisted a core ECG laboratory, (b) (4) to review copies of the paper ECGs obtained at each study site. This additional analysis had been pre-specified in the statistical analysis plan (SAP), dependent on certain criteria relating to change from Baseline in QTcF values being met. All ECGs were blinded with respect to subject identifiers and visit prior to core laboratory analysis. Interval duration measurements were determined by a single trained analyst, including RR, PR, QRS and QT intervals, using manual caliper placement on 3 consecutive beats. A cardiologist then verified the interval durations and performed a morphology analysis, noting any T-U wave complexes that were compatible with an effect on cardiac repolarization. Heart rate and the corrected QT interval based on Fridericia's formula were calculated from the data.

Mean change in QTcF ranged between -9 msec at Week 10 and +3 msec at Week 18. Due to the small sample size and the variability in QTc measurements across subjects, the 90% CIs of the estimates were relatively wide. At Week 18, with mean change in QTcF of 3 msec, the upper

bound of the 90% CI somewhat exceeded 10 msec (11.7 msec). At subsequent visits, mean change in QTcF was lower and the upper bounds of the CIs were <10 msec. Importantly, none of the subjects had treatment-emergent QTcF >500 msec or a change from Baseline >60 msec based on central review.

Electrocardiograms: Elevated LDL-C and Other Risk Factors Study Pool

Descriptive statistics for Baseline values and change from Baseline to maximum increased or decreased value on study in ECG parameters are presented; results are based on site-reported data.

Review of changes from Baseline to the maximum increased or decreased value on study in QTc showed that the magnitude of mean and median changes to maximum increase and maximum decrease were relatively similar. Both higher mean increases and decreases were seen in the high-dose group (10.3 and -9.2 msec, respectively) compared to the other lomitapide dose groups; however these was no apparent dose response for change from Baseline in this parameter. The mean changes from Baseline to maximum increase or decrease on study in other ECG parameters were relatively similar in the lomitapide, placebo, and active control groups.

Deaths: Across the lomitapide clinical program, 1 death was reported among 1145 subjects, including 925 subjects who received lomitapide. The death was reported in Subject 04-1049 in Study AEGR-733-001 who received lomitapide. The subject died of myocardial infarction 1 week post-treatment; the event was assessed as unrelated to study treatment. The subject was a 54- year-old Caucasian male with medical history significant for deep vein thrombosis, peptic ulcer, Factor V Leiden, and hypertension. Prior and concomitant medications included atenolol 50 mg PO for hypertension and aspirin 81 mg PO for cardiac prophylaxis. He received lomitapide for 84 days.

Reviewer's comments: No syncope, seizures, sudden cardiac deaths or ventricular arrhythmias linked to lomitapide were reported in the studies. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features lomitapide's of clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 50,820. The sponsor submitted the study report AEGR-733-011 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, 5-Period Crossover Study to Define the Electrocardiographic (ECG) Effects of Lomitapide using Single Therapeutic and Supratherapeutic Doses, and Co-administration with Ketoconazole, Compared to Placebo, Ketoconazole Alone, and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Study (AEGR-733-011).

4.2.2 Protocol Number

AEGR-733-011

4.2.3 Study Dates

Study Start Date: 10 May 2011
Study End Date: 30 September 2011

4.2.4 Objectives

The primary objective of the study was to determine that single 75 and 200 mg solution doses of lomitapide, and 75 mg (in solution) co-administered with ketoconazole (when adjusted for the effects of ketoconazole administration alone), do not differ from placebo in the mean change from baseline in 12-lead electrocardiogram QT interval measurements (after performing appropriate QT correction for heart rate).

The secondary objectives were:

- To evaluate the relationship between plasma lomitapide and ketoconazole concentrations and QTc interval
- To further evaluate the safety and tolerability of lomitapide when given as single therapeutic and supratherapeutic doses of 75 and 200 mg, respectively, and 75 mg co-administered with ketoconazole.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, randomized, 6-treatment, 5-period, crossover study.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin and ketoconazole) controls.

4.2.5.3 Blinding

This study was double-blinded for lomitapide and placebo, and open-label for the ketoconazole and moxifloxacin.

4.2.5.4 Treatment Arms

This study includes 6 treatments:

- lomitapide 75 mg
- lomitapide 200 mg
- lomitapide 75 mg co-administered with ketoconazole
- placebo
- ketoconazole 200 mg
- moxifloxacin 400 mg

4.2.5.5 Sponsor's Justification for Doses

"A therapeutic dose of 75 mg lomitapide administered orally as a solution was selected based on the PK of lomitapide."

"Assuming linearity in PK, as observed in all other studies, the projected maximum observed plasma concentration (C_{max}) for a 75 mg solution dose is 8 to 9 ng/mL, approximately the steady state C_{max} following 50 mg multiple oral capsule dosing (8.5 ng/mL). The highest oral single dose of lomitapide administered to subjects or patients is 200 mg."

"This crossover study was performed in healthy subjects. A supratherapeutic dose of lomitapide (75 mg co-administered with ketoconazole) was selected to mimic the exposure that could occur in the target population in the worst circumstances (e.g., concomitant liver disease, taking more than the clinical dose prescribed, concomitant use with an inhibitor of CYP 3A4). As inhibition of CYP 3A4 will reduce exposure to metabolites of lomitapide, a solution dose of 200 mg lomitapide was administered to maximize exposure to the primary metabolites of lomitapide, M1 and M3. The C_{max} for lomitapide following administration of 200 mg as an oral solution was projected to be 25 ng/mL."

"A 200 mg ketoconazole dose was selected because 200 mg administered every 12 hours has been shown to be sufficient to attain maximum CYP 3A4 inhibition.

"A 400 mg dose of moxifloxacin was selected because this dose in commonly used in thorough QTc studies."

"Lomitapide elimination is primarily biliary (~60%) and renal (~33%). No unchanged drug excreted is excreted in urine with ~7% in feces. *In vitro* results suggest lomitapide is metabolized by CYP3A4 and *in vitro* is a direct inhibitor of CYP3A4. The IC50s in vitro were 1000 times greater than those achieved clinically. There are two known primary metabolites that are inactive: M1 (BMS-203215); M3 (BMS-203304)."

(Source: Clinical Study Report No. AEGR-733-011, Section 9.4.4, Pg 24)

Reviewer's Comments: QT-IRT protocol review for lomitapide concluded that the choice of doses for the TQT study was acceptable. Based on the gathered clinical experience of lomitapide, the supratherapeutic dose selected for the TQT study is reasonable. The exposure obtained by the supratherapeutic dose selected (200 mg, solution) is higher than what has been observed in the repeated administration of a therapeutic dose of 60-mg oral capsule once daily (~16 fold for C_{max} and ~4 fold for AUC).

With respect to concomitant administration of ketoconazole, the 200-mg dose given as a solution twice a day is appropriate as maximum CYP3A4 inhibition is generally observed after two doses of ketoconazole. The scenario would represent the expected high clinical exposure scenario. The exposure obtained by the concomitant administration of ketoconazole with therapeutic dose selected (75 mg, solution) in this TQT study is higher than what has been observed in the repeated administration of a therapeutic dose of 50-mg oral capsule once daily for 14 days (~11.2-fold for C_{max} and ~10.6-fold for AUC). Furthermore, it is important to note that the use of moderate or strong CYP3A4 inhibitor use is contraindicated in the proposed label.

The dose chosen for moxifloxacin to conduct the TQT study is appropriate.

4.2.5.6 Instructions with Regard to Meals

"All doses were administered orally. On Days 1 and 3, subjects received a light breakfast snack at approximately 1 hour and 15 minutes prior to dosing; the snack was to be consumed within 15 minutes of serving."

(Source Clinical Study Report No. AEGR-733-011, Section 9.4.5, Pg 24)

Reviewer's Comment: The sponsor proposes that lomitapide be administered should be administered once daily at bedtime, with a glass of water and without food (as food increases the exposure of lomitapide and may adversely impact gastrointestinal tolerability). The food effect study resulted in a +77% mean change in C_{max} and +58% mean change in AUC compared to fasted state when 50 mg of lomitapide was administered with a high-fat meal.

According to the study protocol, a breakfast snack was given on Days 1 and 3 prior to dosing followed by a fast from food (not including water) for at least 4 hours postdose. The sponsor states the reason for administering the dose after consumption of food is that food may increase lomitapide exposure and the study aims to maximize lomitapide plasma concentrations without affecting the study objectives.

For the purposes of the study, the administration of lomitapide in a non-fasting state would increase exposure, thereby maximizing exposure for the study. As the timing with respect to dose and type of food given was not controlled in the study, the PK variability in lomitapide exposure would inevitably increase. Nonetheless, the reviewer concurs with the administration of food as appropriate for the purposes of the study.

4.2.5.7 ECG and PK Assessments

Study Day	-1	Period 1 through 5, Days 1-3 (therapeutic: 75 mg, supra-therapeutic: 200 mg)
Intervention	No treatment (Baseline)	Therapeutic: single dose of 75 mg oral lomitapide solution. Supra-therapeutic: single dose of 200 mg oral lomitapide solution. With Ketoconazole: single dose of 75 mg oral lomitapide + BID 200 mg ketoconazole. Ketoconazole alone: BID 200 mg ketoconazole. Moxifloxacin: single PO dose of 400 mg.
12-Lead ECGs	None collected	Continuous recording in up to 10 replicates at each timepoint on Days 1 and 3 of each treatment period. Pre-treatment timepoints were obtained prior to the first dose on Day 1 of each treatment period at -45 minutes, -30 minutes, and -15 minutes. Postdose timepoints occurred at the following times from the first dose on Days 1 and 3 in each period of the study: 1, 2, 3, 4, 5, 7, 12, and 24 hours postdose.
PK Samples for drug	None collected	Pre-dose (within 15 min prior to dosing) and at 1, 2, 3, 4, 5, 7, 12 and 24-h post-dose.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT effect at peak concentrations of lomitapide. The median T_{max} obtained in the study was ~2.0 h and 3.0 h for the therapeutic and supratherapeutic doses of lomitapide, respectively, and is within the expected range of 2.8 h upon dosing of lomitapide solution.

4.2.6 Baseline

The sponsor used time-averaged baseline QTc values on Day 1.

4.2.7 ECG Collection

Continuous Holter monitoring of electrocardiographic parameters was performed during the study. Electrocardiograms were obtained using a high frequency 12-lead digital Global Instrumentation (M12R) Holter/ECG device for continuous recordings on Days 1 and 3 of each treatment period. The ECGs were stored continuously on a flash card and were not available for review until the card was received by the core laboratory and analyzed.

Electrocardiograms used in the analysis were extracted from predetermined timepoints and read centrally using a highly automated measurement technique. In this crossover study using pre-treatment ECGs as the baseline, the continuous ECG recording was started approximately 1 hour prior to the first dose on Day 1 to obtain the pre-treatment ECGs.

Review of all ECGs for a particular subject was performed by the same reader. The primary analysis lead was Lead II. If the primary analysis lead needed to be changed, all data from the subject was analyzed using the new lead.

The (b) (4) core laboratory utilized an advanced algorithm (TQTPlus) to extract ECGs from continuous Holter recordings. During protocol-specified ECG extraction windows, 10-second digital 12-lead ECG tracings were extracted from continuous Holter recordings.

Highly-automated QT (HAQT) analysis was performed in all analyzable (non-artifact) beats in the 10 ECG replicates.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Subjects were 37 males and 19 females aged between 23 and 55 years, and with a BMI between 21.0 and 29.9 kg/m^2. Of the 56 subjects who entered the study, 35 subjects were White, 18 subjects were Black or African American, 2 subjects were Asian, and 1 subject self-reported his race as "Mexican". Twenty-eight of the 56 subjects were Hispanic or Latino.
A total of 6 subjects were withdrawn from the study. Of these, 2 subjects were withdrawn by the investigator due to AEs (ALT and AST increased), 3 subjects withdrew their consent, and 1 subject was withdrawn by the investigator due to failing the drug screen at the Check-in visit for Period 3.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoints were time-matched baseline-adjusted mean differences between 75 mg lomitapide and placebo, between 200 mg lomitapide and placebo, and between 75 mg lomitapide co-administered with ketoconazole and ketoconazole in QTcI. The sponsor used an analysis of covariance (ANCOVA) and the result is presented in Table 2. This model included period, sequence, time, treatment, time-by-period interaction and time-by-treatment interaction as fixed effect terms. Baseline QTcI for each period was included as a covariate, and subject and subject by period as random effects. The upper limits of the 2-sided 90% CI for the 75 mg lomitapide, 200 mg lomitapide, and 75 mg lomitapide co-administered with ketoconazole were below 10 ms.

Table 2: Sponsor Results of ΔΔQTcI

Time Postdose (hr)	Mean	SE	90% CI		Mean	SE	90% CI	
			Lower	Upper			Lower	Upper
	75 mg Lomitapide Adjusted for Placebo				200 mg Lomitapide Adjusted for Placebo			
1	-1.2	0.8	-2.5	0.2	1.8	1.5	-0.7	4.2
2	-1.2	0.8	-2.5	0.1	0.3	1.4	-2.0	2.6
3	-2.1	0.9	-3.6	-0.5	1.9	1.5	-0.5	4.3
4	-1.8	1.0	-3.5	-0.1	-0.1	1.3	-2.2	2.1
5	-1.8	1.0	-3.4	-0.2	-0.1	1.3	-2.2	2.1
7	-2.6	1.2	-4.6	-0.5	1.3	1.2	-0.8	3.3
12	-1.0	0.9	-2.5	0.5	2.8	1.2	0.9	4.7
24	1.4	0.9	-0.2	3.0	1.0	1.3	-1.1	3.1
	75 mg Lomitapide + Ketoconazole Adjusted for Ketoconazole				Ketoconazole Adjusted for Placebo			
1	0.4	1.5	-2.1	2.9	4.7	1.5	2.2	7.2
2	-1.7	1.4	-4.0	0.6	5.9	1.4	3.6	8.2
3	-1.2	1.5	-3.6	1.2	6.5	1.5	4.1	8.9
4	-0.8	1.3	-2.9	1.4	4.1	1.3	2.0	6.2
5	-0.4	1.3	-2.5	1.6	4.2	1.2	2.2	6.3
7	-0.8	1.2	-2.9	1.2	2.7	1.2	0.7	4.7
12	0.6	1.2	-1.4	2.5	2.4	1.2	0.5	4.3
24	2.3	1.2	0.3	4.4	1.1	1.2	-0.9	3.1
	Moxifloxacin Adjusted for Placebo							
1	12.4	1.5	9.9	14.9				
2	10.7	1.4	8.4	13.0				
3	11.6	1.5	9.2	14.0				
4	10.3	1.3	8.2	12.4				
5	8.2	1.3	6.2	10.3				
7	10.0	1.2	8.0	12.0				
12	10.9	1.1	9.0	12.8				
24	6.4	1.2	4.4	8.5				

CI = confidence interval, QTcI = QT interval corrected for heart rate using the individualized formula, ΔΔQTcI = placebo- or ketoconazole-corrected change from baseline in QTcI, SE = standard error.

(Source: Clinical Study Report AEGR-733-011 *Table 11.8., Pg 58/396)*

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our analyses results are similar as provided by the sponsor.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcI effect for moxifloxacin and ketoconazole. The analysis results were presented in Table 2. The largest lower bounds of the 2-sided 90% CI for the mean differences between moxifloxacin and placebo, and between ketoconazole and placebo are 9.9 ms and 4.1 ms, respectively.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 500 ms and ΔQTc >60 ms.

4.2.8.3 Safety Analysis

A total of 34 subjects experienced treatment emergent AEs during the study. Most AEs were mild in severity, with the exception of 1 severe AE which was also considered an SAE. Only 1 subject experienced an SAE: Subject 55 experienced an episode of severe post-traumatic stress disorder following dosing with placebo, which was not considered related to study drugs. The incidence of AEs was greater following dosing with 200 mg lomitapide compared with 75 mg lomitapide. The incidence of AEs was greater following co-administration of 75 mg lomitapide with 200 mg ketoconazole than following dosing of 75 mg lomitapide alone or 200 mg ketoconazole alone.

Two subjects (Subjects 40 and 53) were withdrawn from the study due to AEs of elevated ALT and elevated AST that were considered possibly related to study drugs. The last dose of study drug administered to each subject prior to onset of the AEs was 75 mg lomitapide co-administered with 200 mg ketoconazole.

(Source: CSR # AEGR-733-011, page 74)

Reviewer's comments: No AEs as per ICH E14 guidance were reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3 (lomitapide). Both C_{max} and AUC values in the TQT study were 3.7 and 4-fold, respectively, following administration of 200 mg lomitapide (supra-therapeutic) compared with 75 mg lomitapide, the therapeutic dose in the TQT study. With co-administration with ketoconazole, the C_{max} and AUC values in the thorough QT study were 5.3 and 6.6 -fold, respectively, following administration of 75 mg lomitapide with ketoconazole compared with 75 mg lomitapide. Moxifloxacin pharmacokinetics was not characterized in this study.

Table 3: Sponsor's Summary of Lomitapide Pharmacokinetic Parameters

Parameter	Treatment		
	75 mg Lomitapide (N=53)	200 mg Lomitapide (N=53)	75 mg Lomitapide + 200 mg Ketoconazole (N=54)
AUC_{0-t} (ng·hr/mL)	214 (41.6)	852 (43.4)	1412 (43.0)
C_{max} (ng/mL)	18.1 (46.2)	67.0 (52.3)	95.4 (45.9)
t_{max}[a] (hr)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	4.00 (2.00, 7.00)

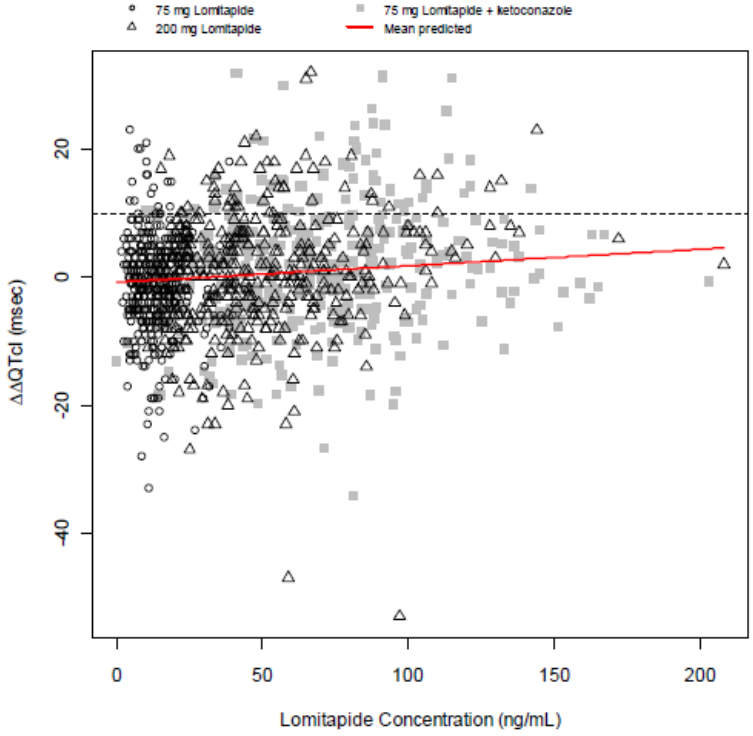
Source: Tables 14.2.2-1a to 14.2.2-1c
AUC_{0-t} = area under the plasma concentration-time curve from hour 0 to the last measurable concentration, C_{max} = maximum observed plasma concentration, N = number of subjects studied, t_{max} = time to the maximum observed plasma concentration.
[a] Median (min-max).
Geometric mean (coefficient of variation [CV%]) data are presented.

(Source Clinical Study Report No. AEGR-733-011, Section 11.4.1, Pg 48, Table 11-1)

4.2.8.4.2 Exposure-Response Analysis

A plot of ΔΔQTc vs. lomitapide concentration is presented in Figure 1 and the parameter estimates for the exposure-response analysis is presented in Table 4.

Figure 1: Mean baseline-adjusted QTcI v Lomitapide Concentrations (Sponsor)



(Source Clinical Study Report No. AEGR-733-011, Section 11.6, Pg 66)

Table 4: Sponsor's Exposure-Response Analysis for Lomitapide vs. ΔΔQTcI

Parameter	Estimate (90% CI)	P-Value	Between-Subject Variation
Intercept (ms)	-0.82 (-1.99, 0.35)	0.2504	4.43
Slope for lomitapide (ms per ng/mL)	0.0258 (0.0018, 0.050)	0.0771	0.0795
Slope for ketoconazole (ms per ng/mL)	0.0013 (0.0010, 0.0017)	< 0.0001	0.0012
Slope for lomitapide-ketoconazole interaction (ms per square ng/mL)	-0.000006 (-0.000011, -0.000001)	0.0378	0.000010
Residual variability (ms)	7.03	--	--

Source: Concentration-ECG Effect Report (Appendix 16.2.6.3: Table 1)
CI = confidence interval, QTcI = QT interval corrected for heart rate using the individualized formula, ΔΔQTcI = placebo- or ketoconazole-corrected change from baseline in QTcI.

(Source Clinical Study Report No. E2007 NAI114346, Section 11.6, Pg 65)

Reviewer's Comments: A plot of ΔΔQTc vs. lomitapide concentration is presented in Figure 1 with an increase in trend for the exposure-response relationship. For the exposure-response analysis, the individual ΔΔQTcI values following co-administration of 75 mg lomitapide with ketoconazole were adjusted for the lomitapide-ketoconazole interaction (Table 4). Accounting for the effects of ketoconazole, significant slope was observed (p-value ~ 0.0378). The estimated population slopes for lomitapide, ketoconazole, and lomitapide-ketoconazole interaction were 0.0258 msec per ng/mL, 0.0013 msec per ng/mL, and -0.000006 msec per ng/mL, respectively. The sponsor concludes that there is a significant relation between increasing plasma levels of lomitapide and the observed ΔΔQTcI effect, but that the slope is shallow. Based on an independent analysis, the reviewer concludes that the relationship between ΔΔQTcI and lomitapide was not significant upon correcting for the effects of placebo and the effects of ketoconazole, analyzed separately.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

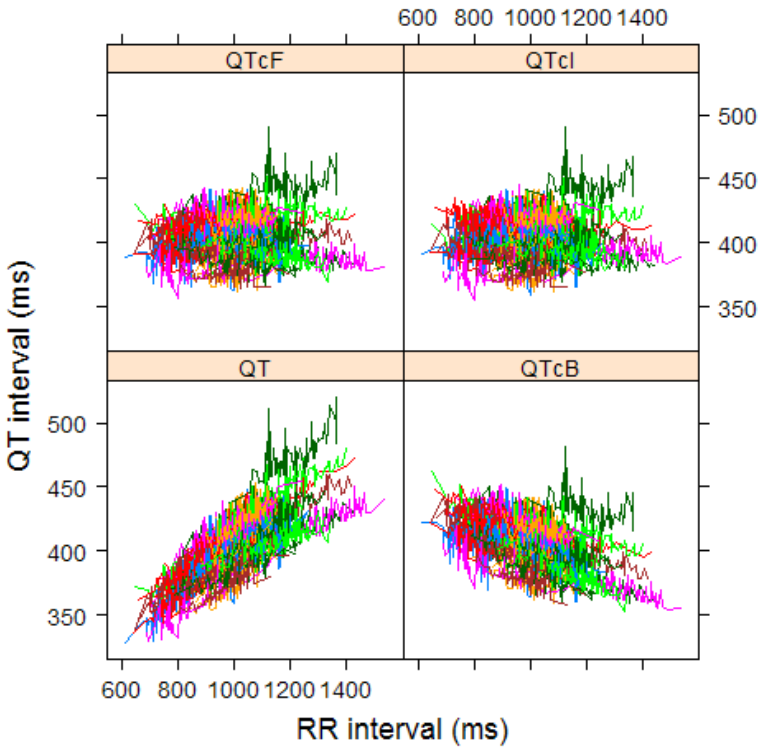
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it appears that QTcI is better than QTcF and QTcB. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
200MG LOMITAPIDE	53	0.0063	53	0.0017	53	0.0012
75MG LOMITAPIDE + KETOCONAZOLE	55	0.0063	55	0.0024	55	0.0016
KETOCONAZOLE	52	0.0052	52	0.0016	52	0.0011
MOXIFLOXACIN	53	0.0063	53	0.0030	53	0.0022
PLACEBO FOR LOMITAPIDE	53	0.0063	53	0.0019	53	0.0015
All	56	0.0046	56	0.0009	56	0.0003

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB), Individual correction (QTcI) and Fridericia (QTcF).

Figure 2: QT, QTcB, QTcI, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 6, Table 7 and Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between 75 mg lomitapide and placebo, between 200 mg lomitapide and placebo, and between 75 mg lomitapide co-administered with Ketoconazole and Ketoconazole are 3.1 ms, 5.4 ms and 5.3 ms, respectively.

Table 6: Analysis Results of ΔQTcI and ΔΔQTcI for 75 mg Lomitapide

	Placebo	75MG LOMITAPIDE		
	ΔQTcI	ΔQTcI	ΔΔQTcI	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
1	-4.5	-5.6	-1.1	(-2.8, 0.6)
2	0.2	-0.9	-1.1	(-2.9, 0.7)
3	1.1	-1.0	-2.1	(-3.9, -0.3)
4	0.9	-1.0	-1.9	(-3.8, 0.1)
5	1.6	-0.2	-1.9	(-3.7, 0.0)
7	1.8	-1.0	-2.8	(-5.3, -0.2)
12	-2.9	-3.7	-0.8	(-2.9, 1.2)
24	-1.8	-0.7	1.1	(-0.8, 3.1)

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI for 200 mg Lomitapide, Ketoconazole and Moxifloxacin 400 mg

	Placebo	200MG LOMITAPIDE				KETOCONAZOLE				MOXIFLOXACIN				
	ΔQTcI	ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
1	-4.6	50	-3.0	1.6	(-1.0, 4.3)	47	-0.2	4.4	(1.7, 7.1)	47	7.9	12.5	(9.8, 15.2)	(8.8, 16.2)
2	1.2	52	1.6	0.4	(-2.4, 3.3)	51	6.9	5.7	(2.8, 8.6)	53	12.0	10.8	(8.0, 13.7)	(6.9, 14.7)
3	0.9	53	3.0	2.1	(-0.6, 4.8)	52	7.4	6.4	(3.7, 9.2)	53	12.6	11.7	(9.0, 14.4)	(8.0, 15.4)
4	1.5	50	1.7	0.1	(-2.6, 2.8)	51	5.5	4.0	(1.3, 6.7)	53	12.0	10.4	(7.8, 13.1)	(6.8, 14.1)
5	2.3	47	2.2	-0.1	(-3.5, 3.4)	51	6.2	3.9	(0.6, 7.3)	51	10.5	8.2	(4.9, 11.6)	(3.6, 12.9)
7	-4.3	49	-3.4	1.0	(-1.7, 3.6)	50	-2.0	2.3	(-0.3, 5.0)	52	5.4	9.8	(7.2, 12.4)	(6.2, 13.3)
12	-4.5	52	-1.7	2.8	(0.3, 5.4)	52	-2.2	2.3	(-0.2, 4.9)	53	6.5	11.1	(8.5, 13.6)	(7.6, 14.5)
24	-0.0	39	1.4	1.5	(-1.2, 4.1)	44	1.1	1.1	(-1.4, 3.7)	41	6.1	6.1	(3.5, 8.7)	(2.6, 9.6)

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for 75 mg Lomitapide co-administered with Ketoconazole

	KETOCONAZOLE	75MG LOMITAPIDE + KETOCONAZOLE			
	ΔQTcI	ΔQTcI		ΔΔQTcI	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1	-0.2	50	0.8	1.1	(-1.6, 3.7)
2	6.9	52	5.6	-1.3	(-4.2, 1.5)
3	7.4	53	6.6	-0.7	(-3.4, 2.0)
4	5.5	53	5.2	-0.4	(-3.1, 2.3)
5	6.2	52	6.7	0.5	(-2.9, 3.8)
7	-2.0	53	-2.5	-0.4	(-3.0, 2.2)
12	-2.2	50	-1.2	1.0	(-1.6, 3.5)
24	1.1	45	3.8	2.7	(0.2, 5.3)

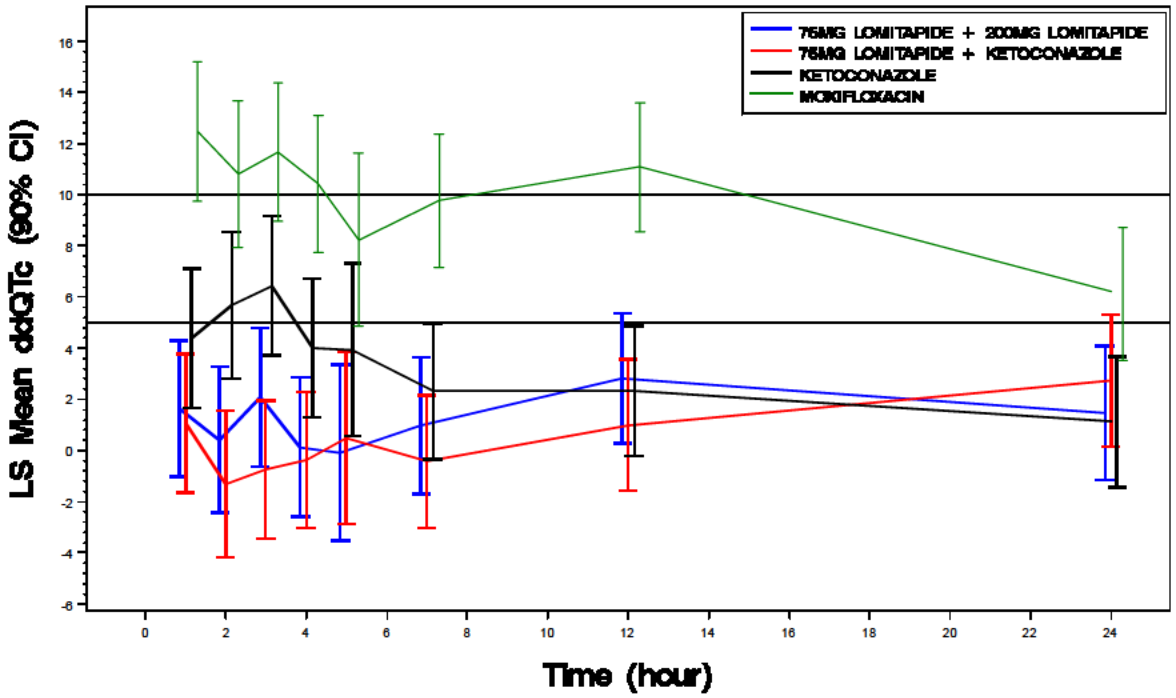
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 9.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.8 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcI Over Time

Figure 3 displays the time profile of ΔΔQTcI for lomitapide groups, lomitapide co-administered with Ketoconazole, Ketoconazole and moxifloxacin 400 mg.

Figure 3: Mean and 90% CI ΔΔQTcI Time Course for lomitapide groups, Ketoconazole and moxifloxacin 400 mg



Reviewer's comments: The rising phase for moxifloxacin is missing in this study. We would like to evaluate either 15 minutes or 30 minutes after administration of moxifloxacin.

5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are ≤450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcI is above 500 ms.

Table 9: Categorical Analysis for QTcI

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms
200MG LOMITAPIDE	53	52 (98.1%)	1 (1.9%)	0 (0.0%)
75MG LOMITAPIDE + KETOCONAZOLE	55	54 (98.2%)	1 (1.8%)	0 (0.0%)
KETOCONAZOLE	52	50 (96.2%)	2 (3.8%)	0 (0.0%)
MOXIFLOXACIN	53	52 (98.1%)	0 (0.0%)	1 (1.9%)
PLACEBO FOR LOMITAPIDE	53	52 (98.1%)	1 (1.9%)	0 (0.0%)

Table 10 lists the categorical analysis for ΔQTcI. No subject's change from baseline is above 60 ms.

Table 10: Categorical Analysis for ΔQTcI

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
200MG LOMITAPIDE	53	53 (100%)	0 (0.0%)
75MG LOMITAPIDE + KETOCONAZOLE	54	52 (96.3%)	2 (3.7%)
KETOCONAZOLE	52	52 (100%)	0 (0.0%)
MOXIFLOXACIN	53	50 (94.3%)	3 (5.7%)
PLACEBO FOR LOMITAPIDE	52	50 (96.2%)	2 (3.8%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11, Table 12 and Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between 75 mg lomitapide and placebo, between 200 mg lomitapide and placebo, and between 75 mg lomitapide co-administered with Ketoconazole and Ketoconazole are 2.0 bpm, 3.1 bpm and 1.6 bpm, respectively. No subject who experienced HR interval greater than 100 bpm was in lomitapide treatment groups.

Table 11: Analysis Results of ΔHR and ΔΔHR for 75 mg Lomitapide

	Placebo	75MG LOMITAPIDE		
	ΔHR	ΔHR	ΔΔHR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
1	2.8	2.4	-0.4	(-1.6, 0.7)
2	1.9	1.3	-0.6	(-2.0, 0.9)
3	0.8	1.1	0.3	(-1.1, 1.8)
4	-1.3	-1.0	0.4	(-1.0, 1.8)
5	0.1	0.8	0.6	(-0.7, 2.0)
7	8.3	8.5	0.2	(-1.3, 1.7)
12	3.4	3.3	-0.1	(-1.5, 1.3)
24	-0.1	-0.1	-0.0	(-1.5, 1.5)

Table 12: Analysis Results of ΔHR and ΔΔHR for 200 mg Lomitapide, Ketoconazole and Moxifloxacin 400 mg

	Placebo	200MG LOMITAPIDE			KETOCONAZOLE			MOXIFLOXACIN		
	ΔHR	ΔHR	ΔΔHR		ΔHR	ΔΔHR		ΔHR	ΔΔHR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
1	3.1	4.6	1.5	(0.0, 3.1)	4.8	1.7	(0.2, 3.3)	5.2	2.1	(0.5, 3.6)
2	1.1	2.0	0.9	(-0.7, 2.5)	2.2	1.1	(-0.6, 2.7)	1.9	0.9	(-0.8, 2.5)
3	-0.0	0.7	0.7	(-0.8, 2.3)	1.0	1.1	(-0.5, 2.6)	0.3	0.4	(-1.2, 1.9)
4	1.3	1.4	0.1	(-1.6, 1.9)	1.6	0.3	(-1.4, 2.0)	1.4	0.1	(-1.6, 1.8)
5	7.7	7.3	-0.4	(-2.3, 1.5)	8.5	0.8	(-1.1, 2.7)	7.6	-0.2	(-2.1, 1.7)
7	6.1	5.5	-0.7	(-2.4, 1.1)	6.4	0.3	(-1.5, 2.0)	6.3	0.2	(-1.6, 1.9)
12	5.1	4.4	-0.7	(-2.4, 0.9)	6.7	1.5	(-0.1, 3.2)	6.6	1.5	(-0.1, 3.2)
24	1.3	1.4	0.1	(-1.6, 1.7)	2.0	0.7	(-0.9, 2.3)	0.9	-0.4	(-2.0, 1.3)

Table 13 : Analysis Results of ΔHR and ΔΔHR for 75 mg Lomitapide co-administered with Ketoconazole

KETOCONAZOLE		75MG LOMITAPIDE + KETOCONAZOLE			
	ΔHR	ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1	4.8	50	4.0	-0.8	(-2.4, 0.7)
2	2.2	52	2.1	-0.0	(-1.7, 1.6)
3	1.0	53	0.8	-0.3	(-1.8, 1.3)
4	1.6	53	0.8	-0.8	(-2.5, 0.8)
5	8.5	52	7.5	-1.0	(-2.9, 0.9)
7	6.4	53	5.3	-1.1	(-2.8, 0.6)
12	6.7	50	4.4	-2.2	(-3.9, -0.6)
24	2.0	45	0.9	-1.1	(-2.8, 0.5)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14, Table 15 and Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between 75 mg lomitapide and placebo, between 200 mg lomitapide and placebo, and between 75 mg lomitapide co-administered with Ketoconazole and Ketoconazole are 3.1 ms, 7.2 ms and 5.2 bpm, respectively. Table 17 presents the categorical analysis of PR. One subject who experienced PR interval greater than 200 ms was in both 200 mg lomitapide and 75 mg lomitapide co-administered with Ketoconazole group.

Table 14: Analysis Results of ΔPR and ΔΔPR for Lomitapide 75 mg

	Placebo	75MG LOMITAPIDE		
	ΔPR	ΔPR	ΔΔPR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
1	-2.3	-2.1	0.2	(-1.4, 1.8)
2	-4.8	-4.5	0.2	(-1.6, 2.0)
3	-6.5	-5.8	0.7	(-1.3, 2.6)
4	-3.7	-3.2	0.4	(-1.2, 2.1)
5	-5.3	-5.3	0.0	(-1.7, 1.7)
7	-5.2	-4.1	1.1	(-0.9, 3.1)
12	-6.3	-5.8	0.5	(-1.8, 2.8)
24	-3.8	-3.7	0.1	(-1.8, 2.0)

Table 15: Analysis Results of ΔPR and ΔΔPR for Lomitapide 200 mg, Ketoconazole and Moxifloxacin 400 mg

	Placebo	200MG LOMITAPIDE			KETOCONAZOLE			MOXIFLOXACIN		
	ΔPR	ΔPR	ΔΔPR		ΔPR	ΔΔPR		ΔPR	ΔΔPR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
1	0.8	1.0	0.3	(-2.5, 3.0)	1.4	0.6	(-2.2, 3.5)	-0.4	-1.2	(-4.0, 1.6)
2	-0.2	0.8	1.0	(-1.6, 3.6)	-0.5	-0.2	(-2.8, 2.4)	-3.3	-3.0	(-5.6, -0.5)
3	0.1	1.6	1.5	(-1.5, 4.6)	-0.9	-1.0	(-4.0, 2.1)	-4.1	-4.1	(-7.2, -1.1)
4	-1.0	1.6	2.6	(-0.5, 5.8)	-0.1	0.9	(-2.2, 4.1)	-2.6	-1.6	(-4.7, 1.5)
5	0.0	1.8	1.7	(-1.4, 4.9)	0.9	0.9	(-2.2, 4.0)	-2.4	-2.5	(-5.6, 0.7)
7	-4.7	-0.5	4.2	(1.3, 7.2)	-3.7	1.1	(-1.8, 4.0)	-7.3	-2.6	(-5.5, 0.3)
12	-2.5	-3.5	-1.1	(-3.9, 1.7)	-4.9	-2.4	(-5.2, 0.4)	-4.9	-2.4	(-5.2, 0.4)
24	-0.8	-0.7	0.1	(-3.4, 3.6)	0.7	1.4	(-2.0, 4.8)	-1.4	-0.6	(-4.1, 2.9)

Table 16: Analysis Results of ΔPR and ΔΔPR for 75 mg Lomitapide co-administered with Ketoconazole

	Placebo	75MG LOMITAPIDE + KETOCONAZOLE			
		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1	1.4	50	-0.9	-2.3	(-5.1, 0.6)
2	-0.5	52	0.1	0.6	(-2.0, 3.2)
3	-0.9	53	-0.3	0.6	(-2.4, 3.6)
4	-0.1	53	1.1	1.2	(-1.9, 4.3)
5	0.9	52	1.0	0.0	(-3.1, 3.1)
7	-3.7	53	-1.3	2.4	(-0.5, 5.2)
12	-4.9	50	-3.5	1.4	(-1.5, 4.2)
24	0.7	45	-3.6	-4.2	(-7.7, -0.8)

Table 17: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
200MG LOMITAPIDE	53	52 (98.1%)	1 (1.9%)
75MG LOMITAPIDE + KETOCONAZOLE	55	54 (98.2%)	1 (1.8%)
KETOCONAZOLE	52	52 (100%)	0 (0.0%)
MOXIFLOXACIN	53	53 (100%)	0 (0.0%)
PLACEBO FOR LOMITAPIDE	53	52 (98.1%)	1 (1.9%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in

Table 18, Table 19 and Table 20. The largest upper bounds of the 2-sided 90% CI for the mean differences between 75 mg lomitapide and placebo, between200 mg lomitapide and placebo, and between 75 mg lomitapide co-administered with Ketoconazole and Ketoconazole are 0.8 ms, 1.5 ms and 0.2 ms, respectively. Table 21 presents the categorical analysis of QRS. Twenty-nine subjects who experienced QRS interval greater than 110 ms were in 200 mg lomitapide and 75 mg lomitapide co-administered with Ketoconazole.

Table 18: Analysis Results of ΔQRS and ΔΔQRS for 75 mg Lomitapide

	Placebo	75MG LOMITAPIDE		
	ΔQRS	ΔQRS	ΔΔQRS	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI
1	-0.5	-0.4	0.1	(-0.2, 0.5)
2	-0.2	-0.2	-0.0	(-0.3, 0.3)
3	-0.2	-0.1	0.1	(-0.2, 0.5)
4	-0.3	-0.0	0.3	(-0.1, 0.6)
5	-0.2	-0.1	0.1	(-0.3, 0.5)
7	-0.2	-0.4	-0.2	(-0.8, 0.4)
12	-1.1	-0.7	0.4	(-0.1, 0.8)
24	-0.3	-0.4	-0.1	(-0.8, 0.5)

Table 19: Analysis Results of ΔQRS and ΔΔQRS for 200 mg Lomitapide, Ketoconazole and Moxifloxacin 400 mg

	Placebo	200MG LOMITAPIDE			KETOCONAZOLE			MOXIFLOXACIN		
	ΔQRS	ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS		ΔQRS	ΔΔQRS	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
1	-0.1	0.1	0.2	(-0.5, 0.9)	0.1	0.2	(-0.6, 0.9)	0.4	0.5	(-0.2, 1.2)
2	-0.2	0.6	0.7	(0.0, 1.5)	0.6	0.8	(0.0, 1.5)	0.5	0.7	(-0.0, 1.4)
3	-0.0	0.6	0.7	(-0.1, 1.4)	0.3	0.4	(-0.3, 1.1)	0.6	0.6	(-0.1, 1.3)
4	0.0	0.5	0.5	(-0.3, 1.3)	0.3	0.3	(-0.5, 1.0)	0.3	0.2	(-0.5, 1.0)
5	0.0	0.5	0.5	(-0.4, 1.3)	0.4	0.3	(-0.5, 1.2)	0.2	0.1	(-0.7, 1.0)
7	-1.2	-0.5	0.7	(-0.1, 1.4)	-0.4	0.8	(0.0, 1.6)	-0.6	0.6	(-0.2, 1.4)
12	-0.8	-0.4	0.4	(-0.4, 1.2)	-0.3	0.5	(-0.3, 1.3)	-0.3	0.5	(-0.3, 1.3)
24	-0.1	0.3	0.4	(-0.4, 1.2)	0.3	0.4	(-0.4, 1.2)	0.2	0.4	(-0.4, 1.2)

Table 20: Analysis Results of ΔQRS and ΔΔQRS for 75 mg Lomitapide co-administered with Ketoconazole

	Placebo	75MG LOMITAPIDE + KETOCONAZOLE			
	ΔQRS	ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
1	0.1	50	-0.4	-0.5	(-1.2, 0.2)
2	0.6	52	-0.4	-1.0	(-1.7, -0.2)
3	0.3	53	-0.3	-0.6	(-1.3, 0.1)
4	0.3	53	-0.2	-0.5	(-1.3, 0.2)
5	0.4	52	-0.4	-0.8	(-1.6, 0.0)
7	-0.4	53	-1.4	-1.0	(-1.8, -0.3)
12	-0.3	50	-1.0	-0.7	(-1.5, 0.1)
24	0.3	45	-0.4	-0.7	(-1.5, 0.1)

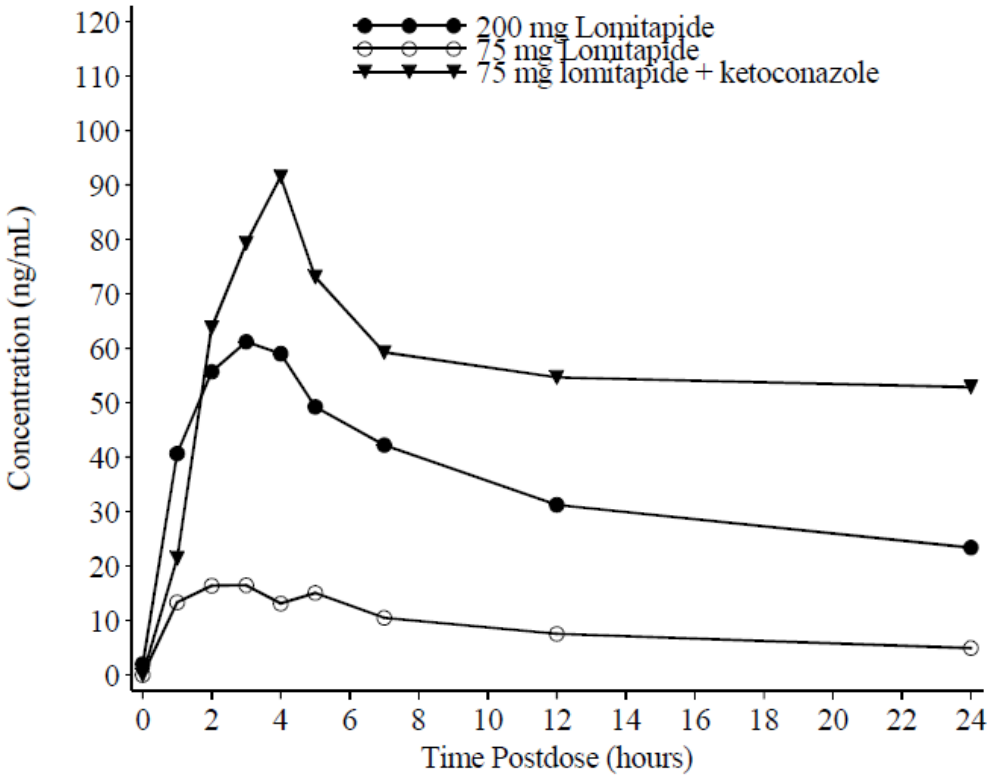
Table 21: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
200MG LOMITAPIDE	53	29 (54.7%)	24 (45.3%)
75MG LOMITAPIDE + KETOCONAZOLE	55	32 (58.2%)	23 (41.8%)
KETOCONAZOLE	52	27 (51.9%)	25 (48.1%)
MOXIFLOXACIN	53	27 (50.9%)	26 (49.1%)
PLACEBO FOR LOMITAPIDE	53	28 (52.8%)	25 (47.2%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

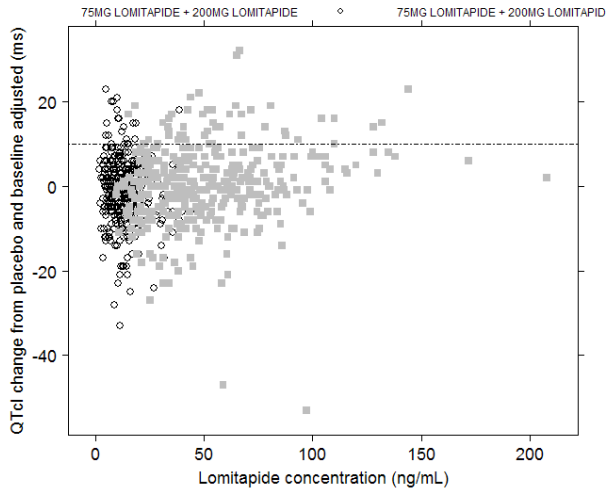
The mean lomitapide concentration-time profile is illustrated in Figure 4.

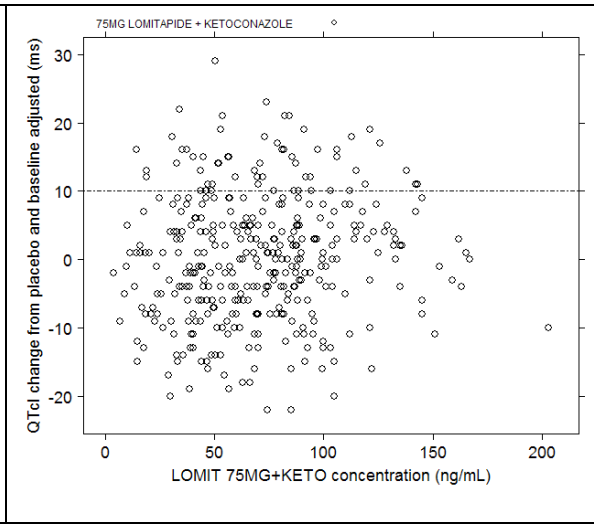
Figure 4: Geometric Mean lomitapide concentration-time profiles for 75 mg lomitapide (open circles), 200 mg lomitapide (closed circles) and 75 mg lomitapide+ ketoconazole (triangles) oral administration



The relationship between ΔΔQTcI and lomitapide concentrations is visualized in Figure 5. No exposure-response relationship was observed for lomitapide upon correction for either placebo or ketoconazole.

Figure 5: (LEFT) Scatterplot Showing Relationship Between ΔΔ QTcI vs. Lomitapide Concentrations adjusted for placebo (open circles and grey squares represent exposures at 75 mg and 200 mg, respectively) and (RIGHT) Relationship Between ΔΔ QTcI vs. Lomitapide Concentrations (ketoconazole corrected)





The estimate of slope and intercept for the relationship between ΔΔQTcI (placebo corrected QTcI or ketoconazole corrected) and lomitapide concentrations is shown in Table 22. There was a modest trend of increasing ΔΔQTcI for the left figure but the relationship was shallow and slope was not statistically significant.

Table 22: Estimates of Intercept and Slope for the Relationship Between Lomitapide Concentrations and ΔΔQTcI

Group	Intercept (ms)	Slope (ms per ng/mL)
Lomitapide Alone	-1.42	0.034
Lomitapide (75 mg) + Ketoconazole	-0.031	0.0022

* Intercepts and slopes for both models were not statistically significant

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

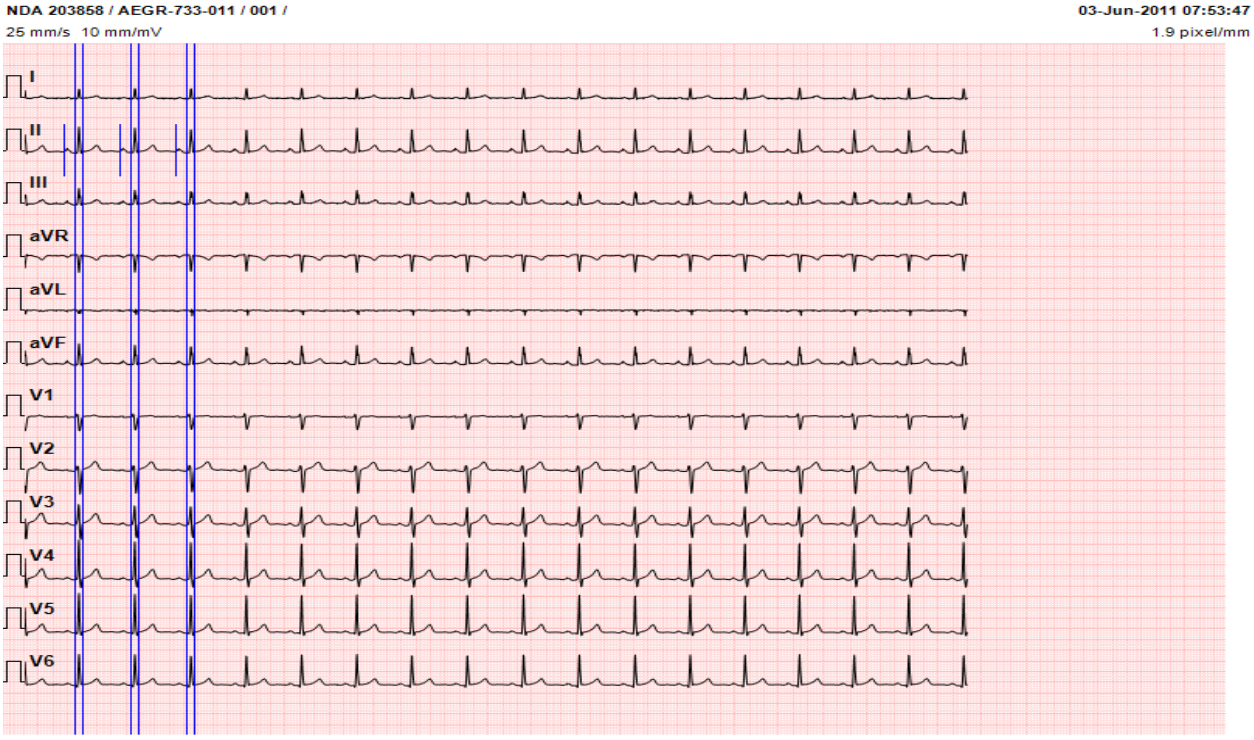
None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 75% of the ECGs were annotated in the primary lead II, with less than 0.3% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

Measurements of PR and QRS intervals, as well as categorical T-wave morphology analysis were performed fully manually in 3 of the 10 ECG replicates with the highest signal to noise ratio at each timepoint.

While PR intervals were annotated in primary lead II, QRS intervals were annotated in all leads.



5.4.3 PR and QRS Interval

One subject had a PR >200 ms but was not clinically meaningful (postbaseline PR 207 ms).

Twenty nine subjects had QRS > 110 ms at baseline without post-baseline increases.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	The recommended starting dose is 5 mg. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg.				
Maximum Tolerated Dose	Stepwise escalation (5 mg x 2 wks, 10 mg x 4 wks, 20 mg x 4 wks, 40 mg x 4 wks, 60 mg) to individualized MTD or a maximum dose of 60 mg.				
Principal adverse events	The most common AEs, reported by eight or more of the 29 patients in the Phase 3 study, included abdominal pain or discomfort, nausea, vomiting, diarrhea, and constipation. Other common AEs (in 5 or more patients) included weight loss, flatulence, abdominal distension, ALT increased, chest pain and nasopharyngitis				
Maximum dose Tested	Single Dose	200 mg (capsule) 60 mg (IV)			
	Multiple Dose	50 mg qd x 14d			
Exposures Achieved at Maximum Tested Dose		Mean C_{max} (ng/mL)	%CV	Mean AUC (h*ng/mL)	%CV
	Single Dose (200 mg, capsule) Single IV Dose (60 mg)	17.3 350.7	44.5 28.8	719.9 1776.5	54.0 11.3
	Multiple Dose (50 mg qd x14 d)	8.5	91.7	132.5 (AUCτ)	92.5
Range of Linear PK	Linearity approached at doses greater than 25 mg qd				
Accumulation at steady-state	3.31 (50 mg QD x 14 d)				
Metabolites	Known primary metabolites (inactive): M1 (BMS-203215); M3 (BMS-203304)				
Absorption	Absolute Bioavailability [IV study]	Mean = 7% %CV=33.8%			
	T_{max} (SAD, capsule)	Parent: Median = 8.0 hr M1: Median = 6.0 hr M3: Median = 2.5 hr			
	T_{max} (Solution)	Parent Median = 2.8 hr M1: Median = 4.2 hr M3: Median = 1.5 hr			
Distribution	Vd (IV)	1200 L			
	% bound	>99.5%			

Elimination	Route	Primary: Biliary (~60%) and Renal (~33%).No unchanged drug excreted in urine; ~7% in feces
	Terminal $t_{1/2}$ (50 mg, SAD capsule)	Parent Mean = 34.4 hr; %CV = 32% M1 Mean = 17.6 hr; %CV = 50% M3 Mean = 42.2 hr; %CV = 138%
	CL_T (50 mg, SAD, capsule)	10,222 mL/min
Intrinsic Factors	**Age**	Unknown
	Sex	A direct comparison of lomitapide pharmacokinetics at steady-state between male and female subjects in the same study has not been conducted. Comparison of the mean lomitapide and metabolite plasma concentrations and PK parameters in males and females in the fasted and fed states, following a single dose of lomitapide, revealed no apparent differences between males and females after a single dose.
	Race	Unknown
	Hepatic and Renal Exposure	Hepatic: Hepatic impairment did not change the T_{max} values. A slight increase in exposure (4% for C_{max}, 47% for AUC) was observed in the mild hepatically impaired subjects compared to matched subjects with normal hepatic function. Mean C_{max} and AUC_{0-inf} values for the moderate hepatic impairment group were approximately 361% and 164% higher, respectively, than those observed in healthy matched controls. No change in half-life for lomitapide was observed in hepatically impaired subjects compared to healthy control subjects. The modest increase in exposure observed in subjects with mild hepatic impairment compared with matched healthy control subjects is not considered clinically significant and would be mitigated by the individualized dose escalation regimen proposed for use in the clinical setting. Irrespective of the PK, lomitapide is contraindicated in patients with moderate or severe hepatic impairment in view of the potential effect of the drug on the liver. Renal: Modest changes in lomitapide C_{max} and AUC were observed in subjects with ESRD relative to matched healthy controls. Although the differences observed crossed the predefined statistical criteria in the study protocol, these observations were not considered to be clinically relevant. Any impact of

		diminished renal function on systemic lomitapide PK would be mitigated by the adjustment in dosing over time, designed to accommodate individual patient responsiveness in terms of efficacy and safety. Therefore, no change in the dosing regimen for lomitapide is required for patients with renal impairment.	
Extrinsic Factors	**Drug Interactions**	Lomitapide is metabolized by CYP3A4 and *in vitro* is a direct inhibitor of CYP3A4. The IC_{50}s *in vitro* were 1000 times greater than those achieved clinically. Co-administration of 60 mg lomitapide (at steady-state) with 40 mg simvastatin significantly increased exposure to simvastatin and simvastatin acid. Exposure to simvastatin and simvastatin acid increased approximately 2-fold and 170%, respectively, compared to simvastatin alone. C_{max} for simvastatin and simvastatin acid increased about 2-fold and 160%, respectively. Co-administration of 60 mg lomitapide (at steady-state) with 20 mg atorvastatin led to a 52% and 49% increase in the AUC of atorvastatin acid and 4 OH atorvastatin, respectively. The interaction with statins is most likely due to the competitive inhibition of CYP3A4. Ketoconazole, a strong inhibitor of CYP 3A4, increased lomitapide C_{max} and AUC 15 fold and 27 fold, respectively. When dosed to steady-state, lomitapide had no clinically meaningful impact on the PK of estrogen-containing (EE) oral contraceptive, niacin, ezetimibe, fenofibrate or dextromethorphan, a CYP 2D6 substrate. Lomitapide increased exposure to both the R and S forms of warfarin and increased INR_{max}.	
	Food Effects	**Mean change - C_{max}**	**Mean change - AUC**
	Low fat meal + 50 mg Lomitapide vs. Fasted	+70%	+27.5%
	High fat meal+ 50 mg Lomitapide vs. Fasted	+77%	+57.6%
Expected High Clinical Exposure Scenario	A single 200 mg solution dose (supratherapeutic) of lomitapide results in a mean C_{max} and AUC that are about 16 and 4 times, respectively the expected mean C_{max} and AUC for a 60 mg QD dose at steady state; the metabolites are not biologically active. A 75 mg solution dose of lomitapide + ketoconazole administered at fed state results in a mean lomitapide C_{max} and AUC that are about 23 and 6 times the expected mean C_{max} and AUC for a 60 mg QD dose at fasting steady state, respectively.		
02 February 2012			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOH JEE NG
07/09/2012

JOANNE ZHANG
07/09/2012

SATJIT S BRAR
07/09/2012

NITIN MEHROTRA
07/09/2012

MONICA L FISZMAN
07/09/2012

NORMAN L STOCKBRIDGE
07/09/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203858 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: lomitapide mesylate Dosage Form: Capsules Strengths: 5 mg, 10 mg, 20 mg		
Applicant: Aegerion Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: 2/29/2012 Date of Receipt: 2/29/2012 Date clock started after UN: N/A		
PDUFA Goal Date: 12/29/2012	Action Goal Date (if different): 12/10/2012	
Filing Date: 4/29/2012	Date of Filing Meeting: 4/16/2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of homozygous familial hypercholesterolemia		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	X 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review X Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 50820	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid X Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Submitted in an amendment subsequent to the initial NDA
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) X Medication Guide (MedGuide) X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				Due to OPDP on 10/15/2012
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				Due to OSE/DRISK on 10/15/2012
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
OTC Labeling	**X Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 7/20/2004, 2/7/2007, 5/17/2010 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 6/15/2011 (Clinical); 4/5/2011 (CMC) ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 16, 2012

NDA #: 203858

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: lomitapide mesylate

DOSAGE FORM/STRENGTH: Capsules

APPLICANT: Aegerion Pharmaceuticals

PROPOSED INDICATION: Adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and triglycerides in patients with homozygous familial hypercholesterolemia.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:	Enid Galliers	N
Cross-Discipline Team Leader (CDTL)	Eric Colman, MD		Y
Clinical	Reviewer:	Jim Smith, MD	Y
	TL:	Eric Colman, MD	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Johnny Lau, PhD	Y
	TL:	Jaya Vaidyanathan, PhD	Y
Biostatistics	Reviewer:	Cynthia Liu	Y
	TL:	Todd Sahlroot, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tim Hummer, PhD	Y
	TL:	Karen Davis Bruno, PhD	N
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman, PhD	N
	TL:	Karl Lin, PhD	N
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Xavier Ysern, PhD	Y
	TL:	Su Tran, PhD	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	Steven Hertz	N
	TL:	Christine Garnett	N
OSE/DMEPA (proprietary name)	Reviewer:	Jamie Wilkins Parker	Y
	TL:	Yelena Maslov	Y
OSE/DRISK (REMS)	Reviewer:	Kate Heinrich Oswell Lisy Vega	N N
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Michelle Marsh	N
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers-Biopharm	Reviewer=Elsbeth Chikhale TL= Angelica Dorantes		Y N
Other attendees	Lee Ripper, Associate Director for Regulatory Affairs, ODE II Anne Pariser, MD, Director of Rare Diseases, Office of New Drugs Immediate Office Amy Egan, MD, Deputy Director for Safety, Division of Metabolism and Endocrinology Products Margarita Tossa, Project Manager, Office of Safety and Epidemiology		Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	X Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	X YES ☐ NO

If no, explain:	
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	X YES Date if known: 10/17/2012 ☐ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X ☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS	☐ Not Applicable XFILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable XYES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	X Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curt Rosebraugh, MD

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): Review Classification: X Standard Review ☐ Priority Review

ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
05/09/2012

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203858

Application Type: New NDA

Name of Drug: Lomitapide Capsules (proposed Tradenames, (b) (4))

Applicant: Aegerion Pharmaceuticals

Submission Date: February 29, 2012

Receipt Date: February 29, 2012

1.0 Regulatory History and Applicant's Main Proposals

This compound is an MTP inhibitor initially developed, under IND 50820, by Bristol Myers Squibb for hypercholesterolemia. When preclinical studies showed liver and pulmonary phospholipidosis, the sponsor ceased development. The IND was transferred to Daniel Rader, MD (University of Pennsylvania) in 2001 and subsequently to Aegerion Pharmaceuticals in 2007. Dr. Rader was studying both Heterozygous Familial Hypercholesterolemia (HeFH) and Homozygous Familial Hypercholesterolemia (HoFH) under this single IND. However, he opened up IND 77775 to retain the HoFH indication and transferred the HeFH development program to Aegerion under IND 50820. Eventually, he transferred IND 77775 to Aegerion also.

Orphan drug designation was granted for HoFH on October 23, 2007. Due to limited resources, Aegerion elected to focus on HoFH, and submitted the NDA for that indication.

This initial concern with phospholipidosis has become less of an issue as it appears that the preclinical findings have not translated into a clinical risk. The primary safety issue now appears to be fat accumulation in the liver.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. The deficiencies were very minor and will be addressed during labeling negotiations with the sponsor.

5.0 Appendix

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: none

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The HL currently exceeds the one-half page maximum. We will determine during the review whether the one-half page maximum will be waived.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: none

YES 4. White space must be present before each major heading in HL.

Comment: none

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: none

Selected Requirements of Prescribing Information (SRPI)

NO 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *There is no ADVERSE REACTIONS section heading. This will be corrected during labeling negotiations.*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).
Comment: none

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment: none

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: none

Product Title

YES 10. Product title in HL must be **bolded.**

Comment: none

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *This date will be added when the NDA is approved.*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment: none

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment: none

YES 24. Each contraindication is bulleted when there is more than one contraindication.
Comment: none

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: none

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: none

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *The revision date is currently listed as "2/2012" but should be "02/2012". However, this will be revised to the date the NDA is approved.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment: none

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment: ***none***

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: ***none***

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:none

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:none

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:none

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *The sponsor has used "sub-sections" instead of "subsections". This will be corrected during labeling negotiations.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment: *Verify whether the heading should be left justified. Nothing specific is mentioned in the Labeling Review Tool.*

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment: ***none***

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *Proposed Medicatiion Guide does not appear at the end of the PI. This will be corrected when approved.*

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *Some subsections are referenced (e.g., under DOSAGE AND ADMINISTRATION, "[see Renal Impairment (8.6]" and "[see Hepatic Impairment (8.7]"). These will be corrected during labeling negotiations.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment: none

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: none

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:none

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
05/08/2012