CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Review Addendum

Date:	**12/21/2012**
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
Drug Name(s):	Lomitapide (Juxtapid™)
Therapeutic Class:	Cholesterol-lowering agent
Dosage and Route:	Starting dose is 5 mg once daily, titrated up to 60 mg as tolerated, oral administration
Application Type/Number:	NDA 203858
Supplement # and Date Received:	Email submissions dated December 20 and 21, 2012
Applicant/sponsor:	Aegerion Pharmaceuticals, Inc.
OSE RCM #:	2012-603

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

1 INTRODUCTION

This review documents DRISK's evaluation of the amended lomitapide REMS submitted by Aegerion via email on December 20 and 21, 2012.

2 MATERIALS REVIEWED

2.1 Materials submitted by Aegerion

- REMS document
- Prescriber Training Module
- Prescriber Enrollment Form
- Prescription Authorization Form
- Dear Healthcare Provider letter
- Dear Professional Association letter
- REMS Webpages
- REMS Supporting document

3 DISCUSSION AND RECOMMENDATIONS

DRISK reviewed and provided comments on the revised lomitapide REMS submitted by Aegerion via email on December 20 in response to the Agency's comments included in DRISK review addendum from December 19, 2012. Additional comments were sent to Aegerion on December 21, 2012 followed by a teleconference between Aegerion, the Division of Metabolism and Endocrinology Products (DMEP), and DRISK.

On December 21, 2012 Aegerion submitted via email an amended version of all REMS documents addressing comments from FDA.

DRISK finds the revised lomitapide REMS and REMS Supporting Document acceptable and recommends approval (see attachments).

Initial REMS Approval: 12/2012

NDA 203858

JUXTAPID (lomitapide) capsules

Drug Class: Microsomal Triglyceride Transfer Protein Inhibitor (MTP-I)

Aegerion Pharmaceuticals, Inc. (Aegerion)

101 Main Street Suite 1850

Cambridge, MA 02142

Telephone: 617-500-7795

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

68 Pages have been Withheld in Full as Duplicate REMS Documents (found elsewhere in this Approval Package) immediately following this page.

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

/s/

AMARILYS VEGA
12/21/2012

CYNTHIA L LACIVITA
12/21/2012
concur

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

Risk Evaluation and Mitigation Strategy (REMS) Review Addendum

Date:	**12/19/2012**
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Heinrich Oswell, MA, Health Communications Analyst (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
Division Director	Claudia Manzo, Pharm.D, Director DRISK
Drug Name(s):	Lomitapide
Therapeutic Class:	Cholesterol-lowering agent
Dosage and Route:	Starting dose is 5 mg once daily, titrated up to 60 mg as tolerated, oral administration
Application Type/Number:	NDA 203858
Supplement # and Date Received:	0032 (amendment), received November 20, 2012 (Seq.no. 0031) 0034 (amendment), received December 05, 2012 (Seq.no. 0033)
Applicant/sponsor:	Aegerion Pharmaceuticals, Inc.
OSE RCM #:	2012-603

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

1 INTRODUCTION

This review, an addendum to DRISK review dated November 11, 2012, documents DRISK's review and comments on the revised Lomitapide REMS documents submitted by Aegerion on November 20, 2012 and December 5, 2012.

2 MATERIALS REVIEWED

2.1 Regulatory History

- **November 28, 2012** – The Division of Metabolism and Endocrinology Products (DMEP) and DRISK reconsidered the language in the goal statement, specifically, the underlined text in the following goal statement:

  > "…To limit access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH."

  The proposed revised text for the goal statement is:

  > "…To limit access to therapy with TRADENAME to patients with a (b) (4) consistent with homozygous familial hypercholesterolemia (HoFH)."

  Rationale – There is no consensus on clinical or diagnostic criteria for HoFH. [1] The use of the terms "clinical diagnosis" (b) (4) of HoFH is more consistent with the patient selection process followed by prescribers in clinical practice.

- **December 4, 2012** – DRISK informed Aegerion that there was no need for the *Prescriber's Guide* (originally submitted by Aegerion as one of the prescriber training materials).

  Rationale – The *Training Slides Module* will serve the same purpose. However, DMEP and DRISK agree that an abridged, one-page version of the *Prescriber's Guide* may remain as part of the REMS and could be inserted as the last page of the training module with instructions to the prescriber to print as a reference.

- December 17, 2012 – Office of Regulatory Policy (ORP) recommended removal of the following text from the goal statement the goal statement:

  > "…To educate prescribers about the approved indication for use of lomitapide"

  Rationale – There is not regulatory precedent for a REMS goal requiring prescriber education about the approved indication. DMEP and DRISK concurred with this recommendation.

---

[1] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis. 2012 Aug;223(2):262-8.

2.2 Materials submitted by Aegerion

- **November 20, 2012** submission from Aegerion:
  1) Proposed REMS with Appendices (Prescriber Enrollment Form, (b) (4) Proposed Prescription Authorization Form)
  2) Proposed REMS Supporting Document
- **December 5, 2012** submission from Aegerion:
  1) Proposed REMS Web pages
  2) Proposed Dear Healthcare Provider (HCP) Letter
  3) Proposed Dear Professional Society Letter
  4) Proposed REMS Training Slides Module

3 RECOMMENDATIONS

DRISK recommends that DMEP send Aegerion the revisions to the REMS materials included in section 4 below.

4 COMMENTS TO THE SPONSOR

FDA reviewed the REMS documents submitted on November 20, 2012 and December 5, 2012 and provides the following recommendations:

1) REMS Document – see appended document with comments and tracked changes.
   a. Prescriber Enrollment Form
   b. Prescription Authorization Form
   c. (b) (4) – removed from the REMS
   d. Dear Healthcare Provider (HCP) Letter
   e. Dear Professional Society Letter
   f. (b) (4) – removed from the REMS
   g. REMS Training Slides Module
   h. Prescriber's Guide – There is no need for the *Prescriber's Guide* because the *Training Slides Module* (i.e., Prescriber Training Module) will serve the same purpose. However, DRISK agrees that an abridged, one-page version of the *Prescriber's Guide* may remain as part of the REMS and could be inserted as the last page of the training module with instructions to the prescriber to print as a reference.
   i. REMS Web pages – see appended document with comments and tracked changes.
2) REMS Supporting Document – please align REMS Supporting Document with revised REMS Document.

86 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

AMARILYS VEGA
12/19/2012

CLAUDIA B MANZO
12/19/2012
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION METABOLISM AND ENDOCRINOLOGY PRODUCTS

NDA/BLA #s:	203858
Products:	Juxtapid (lomitapide) 5 mg, 10 mg, and 20 mg
APPLICANT:	Aegerion Pharmaceuticals, Inc.
FROM:	Amy G. Egan, M.D., M.P.H.
DATE:	November 16, 2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Juxtapid (lomitapide) to ensure that the benefits of the drug outweigh the potential risk of hepatotoxicity. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with homozygous familial hypercholesterolemia is approximately 300, based on a prevalence of 1 in 1 million persons. This estimate is based on a 1993 article in Lancet entitled "Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia."[1]

B. Homozygous familial hypercholesterolemia (HoFH) is a life-threatening genetic disease characterized by marked elevations in LDL-C, tendon xanthomas, and premature coronary atherosclerosis. HoFH patients frequently suffer major adverse cardiovascular events such as heart attack and stroke in adolescence and early adulthood. This aggressive and premature

[1]Moorjani, S., M. Roy, et al. (1993). "Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia." Lancet **341**(8856): 1303-1306.

cardiovascular disease often requires interventions such as coronary bypass surgery, coronary stenting, carotid endarterectomy, and aortic valve replacement.

C. When added to background lipid-lowering therapy, Juxtapid (lomitapide) led to mean decrease in LDL-C of 40%. This level of reduction was maintained at 56 weeks (-44%) despite a decrease in background lipid-lowering therapy in some patients. In addition, eight (35%) of the 23 patients who completed the efficacy period were able to achieve an LDL-C level <100 mg/dL at week 26, with one patient achieving an LDL-C level <70 mg/dL.

D. The expected duration of treatment is lifelong.

E. Juxtapid (lomitapide) can cause elevations in transaminases. In the Juxtapid (lomitapide) clinical trial, 34% of patients treated with Juxtapid (lomitapide) had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 times upper limit of normal (ULN). Juxtapid (lomitapide) also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy. Although hepatic failure has not been observed with Juxtapid (lomitapide), hepatic steatosis is a risk factor for steatohepatitis, which can progress over several years to advanced liver disease and cirrhosis. Given the small size and relatively short duration of Juxtapid (lomitapide) exposure in the pivotal trial, it is not surprising that these potential adverse effects have not yet been observed. In addition to the most serious risk of hepatotoxicity, Juxtapid (lomitapide) has been associated with a pre-clinical signal for teratogenicity. Due to its mechanism of action in the small intestine Juxtapid (lomitapide) may reduce the absorption of fat-soluble nutrients (fat-soluble vitamins, β-carotene, and essential fatty acids). Juxtapid (lomitapide) has also been associated with gastrointestinal adverse reactions, including diarrhea, nausea, dyspepsia, and vomiting.

F. Juxtapid (lomitapide) is a new molecular entity.

The elements of the REMS will be elements to assure safe use, including that healthcare professionals who prescribe Juxtapid (lomitapide) are specially certified (ETASU A), pharmacies that dispense Juxtapid (lomitapide) are specially certified (ETASU B), and Juxtapid (lomitapide) will be dispensed to patients with evidence or other documentation of safe-use conditions (ETASU D), an implementation system, and a timetable for submission of assessments of the REMS.

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

/s/

AMY G EGAN
12/20/2012

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
Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	11/08/2012
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK) Kate Heinrich Oswell, MA, Health Communications Analyst (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
Division Director	Claudia Manzo, Pharm.D, Director DRISK
Drug Name(s):	Lomitapide
Therapeutic Class:	Cholesterol-lowering agent
Dosage and Route:	Starting dose is 5 mg once daily, titrated up to 60 mg as tolerated, oral administration
Application Type/Number:	203858
Applicant/sponsor:	Aegerion Pharmaceuticals, Inc.
OSE RCM #:	2012-603 and 2012-1935

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

CONTENTS

1 INTRODUCTION

This review documents DRISK's evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for lomitapide. Aegerion Pharmaceuticals is seeking approval of lomitapide as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce LDL-C, total cholesterol, apo-B, and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH).

1.1 BACKGROUND

Familial Hypercholesterolemia.[1] Familial Hypercholesterolemia (FH) is an autosomal codominant disorder caused by a large number (>1000) of 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. The elevated levels of LDL-C in FH are due to an increase in the production of LDL from Intermediate-density Lipoprotein (IDL) and a delayed removal of LDL from the blood. Patients with HoFH have mutations in both LDL receptor alleles and have much higher LDL-C levels than those with Heterozygous Familial Hypercholesterolemia (HeFH) who have only one mutant allele. Patients with HoFH are categorized in two groups based on the amount of LDL receptor activity measured in their skin fibroblasts: receptor-negative (<2% of normal LDL receptor activity) and receptor-defective (2–25% of normal LDL receptor activity). Most patients with HoFH are diagnosed in childhood and present with cutaneous xanthomas (hands, wrists, elbows, knees, heels, or buttocks), have total cholesterol levels of >500 mg/dL (can be >1000 mg/dL), and have accelerated atherosclerosis. Receptor-negative patients rarely survive beyond the second decade unless treated; receptor-defective patients have a better prognosis but develop atherosclerotic vascular disease by age 30 or sooner. Treatment for patients with HoFH includes a low fat diet, lipid lowering agents and LDL apheresis. Unfortunately, patients with HoFH are minimally responsive to available lipid lowering drugs and, even with maximal pharmacologic doses of these drugs, generally have LDL-C levels >300 mg/dL.

Lomitapide. Lomitapide is an oral microsomal triglyceride transfer protein (MTP) inhibitor. MTP is an intracellular lipid-transfer protein responsible for transferring triglycerides onto apolipoprotein B (apo-B) during the formation of very-low density lipoprotein (VLDL) in the liver and chylomicrons in the intestine. VLDL is the precursor of LDL. Through its potent inhibition of MTP, lomitapide therapy results in a reduction in synthesis and transport of apo-B containing lipoprotein and circulating LDL-C. The proposed dosing regimen is to escalate from 5 mg daily to 60 mg daily, as tolerated, during a 14-week period.

[1] Rader D.J., Hobbs H.H. (2012). Chapter 356. Disorders of Lipoprotein Metabolism. In D.L. Longo, A.S. Fauci, D.L. Kasper, S.L. Hauser, J.L. Jameson, J. Loscalzo (Eds), *Harrison's Principles of Internal Medicine*, 18e. Retrieved October 22, 2012 from http://www.accessmedicine.com/content.aspx?aID=9143689 .

1.2 REGULATORY HISTORY

Following are pertinent milestones in the regulatory history of lomitapide:

- **June18, 1996** – IND 50820 submitted by Bristol-Myers Squibb.
- **August 21, 2002** – IND 50820 transferred to Daniel Rader, MD, University of Pennsylvania (study for the treatment of HoFH).
- **January 27, 2006** – The Office of Orphan Products Development Grant 1R01 FD003098-01 awarded for MTP Inhibitor for Familial Hypercholesterolemia, Marina Cuchel, MD, PhD was the principal investigator.
- **April 13, 2007** – IND 50820 transferred to Aegerion for development of lomitapide for moderate hypercholesterolemia, which included severe refractory hypercholesterolemia.
- **May 16, 2007** – IND 77775 submitted by Daniel Rader, MD, University of Pennsylvania, for HoFH.
- **October 23, 2007** – Orphan drug designation for the treatment of HoFH.
- **February 28, 2008** – IND 77775 transferred to Aegerion from Dr. Rader to facilitate conducting multi-site trials.
- **May 17, 2010** – End of Phase 2 (EOP2) meeting with FDA. FDA expressed concern about potential off-label use and the sponsor agreed to the need of implementation of post-approval supply constraints.
- **March 03, 2011** – Orphan drug designation for the treatment of familial chylomicronemia.
- **June 15, 2011** – The Agency confirmed that a single, pivotal phase 3 study lacking a placebo control arm would not preclude filing or approval of the lomitapide NDA for the HoFH population and that the available exposure data from the single pivotal phase 3 study are sufficient to support an NDA for HoFH. FDA noted that including a "functional HoFH" definition of average fasting LDL > 300 mg/dL on maximally tolerated lipid-lowering therapy closely resembles the severe refractory HeFH population, which would shift the risk:benefit ratio. FDA encouraged the sponsor to provide detailed plans of how distribution would be restricted to the HoFH population studied in the Phase 3 trial, including how documentation of HoFH status would be collected and confirmed, how distribution would be accomplished, and how the system would be monitored for compliance.
- **February 29, 2012** – Submission of NDA 203858 for the use of lomitapide as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce LDL-C, total cholesterol, apo-B, and triglycerides in patients with HoFH.
- **October 17, 2012** – Advisory Committee meeting voted 13:2 in favor of the approval of lomitapide (with a restrictive REMS) for the treatment of HoFH.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Lomitapide, Risk Management Plan, Aegerion, February 29, 2012.
- Division of Metabolism and Endocrinology Products (DMEP), Advisory Committee meeting background document.
- Aegerion, Advisory Committee meeting background document.
- 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): Lomitapide, Review of Sponsor's Product Registry Proposal, October 2, 2012.

3 RESULTS OF REVIEW

3.1 CLINICAL DEVELOPMENT PROGRAM

Lomitapide's clinical development program included 15 phase 1 studies, 6 phase 2 studies, and one phase 3 trial (26 weeks duration) with an extension (up to 56 weeks). Nine hundred fifteen subjects were exposed to lomitapide in the clinical development program. One of the phase 2 studies was a 16-week, single-arm, 6-subject proof-of-concept trial (HoFH Pilot study). The pivotal phase 3 trial included 29 patients with HoFH and the extension of the phase 3 study included 19 patients. The dosing regimen consisted of forced-titration of lomitapide as follows: daily dose of 5 mg for two weeks followed by dose increase to 10, 20, 40, and 60 mg at four weeks intervals as tolerated. The primary study endpoint was the decrease in mean LDL-C.

Efficacy

The evaluation of the efficacy and safety of lomitapide included a pivotal phase 3, single-arm trial including 29 patients with HoFH, a pivotal trial extension, and a pilot phase 2, single-arm, 16-week duration trial including 6 HoFH patients. Lomitapide's clinical development program demonstrated LDL-C reduction in the HoFH population greater than that observed with potent statins. In the pivotal phase 3 trial, the mean LDL-C decreased was 40% (95% CI, 28% to 52%, $p<0.001$) during 26 weeks of treatment with lomitapide. Statistically significant reductions from baseline were observed in total cholesterol, apoB, non-HDL-C, triglycerides, and VLDL-C.

Safety Concerns

Potential Hepatotoxicity. Lomitapide therapy was associated with increased serum transaminases and increased hepatic fat. Thirty-four percent (10/29) of patients with HoFH treated with lomitapide had ALT ≥3x ULN at least once during the pivotal trial; however, none of these subjects had bilirubin levels outside of the normal range. Seventy-eight percent (18/23) subjects in the pivotal trial showed a maximum absolute increase in hepatic fat >5%; 13% or 3 patients had an absolute increase of greater than 20%.

Lomitapide-induced increase in hepatic fat appears to be reversible after short-term (16 weeks) administration in the HoFH Pilot study. Five of the six subjects in the pilot study showed near-complete resolution of hepatosteatosis after discontinuation of lomitapide and a subsequent publication describing the results of this study indicate that, in the remaining subject, hepatic fat returned to baseline 14 weeks after stopping lomitapide.[2]

Teratogenic Risk. Developmental toxicity studies in rats showed decrease in fetal body weight and malformations (abdomen, tail, heart, limbs, anus) at doses lower than human clinical exposure and fetal death, shortened limbs, and brain defects at doses 10-fold higher than the anticipated clinical exposure. Studies in ferrets showed embryonic death, decreased fetal body weight, and malformations (abdomen, tail, limbs, head) at less than clinical dose level. Studies in rabbits showed no effects on survival or development at doses up to three times higher than human clinical exposure. There were no pregnancy exposures in the clinical development program.

3.2 SPONSOR'S INITIAL REMS PROPOSAL

Pre-NDA REMS Discussions. In a 17 May 2010 EOP2 meeting with FDA, Aegerion noted that they would be pursuing submission of an NDA solely for the HoFH population due to financial constraints. The sponsor recognized the potential for unauthorized prescribing and was amenable to the implementation of post-approval supply constraints to ensure that the drug was available only to the HoFH population. In several meetings, DMEP expressed the position that the use of lomitapide outside the HoFH population would require additional clinical studies due to the shift in risk/benefit ratio.

In the background materials for the 15 June 2011 pre-NDA meeting, Aegerion posed the following question: "Aegerion believes that a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use will be important to ensure that drug use is confined to the specific population identified in the proposed label and, further, that risks are minimized in the marketed use of lomitapide. In this briefing package, we outline the elements of the proposed plan. Does the Agency agree . . .?". The agency responded that there was insufficient information at the time to determine whether a REMS would be necessary and, if it would be necessary, what the required elements would be. Aegerion was advised to submit all planned materials with the NDA.

Lomitapide was submitted with a proposed REMS addressing the risks of potential hepatotoxicity and teratogenicity addressed under the Warnings & Precautions sections of the product label (no boxed warning). Following is a description of the sponsor's REMS proposal.

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

[2] Cuchel M, *et al.* Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med*. 2007 Jan 11; 356(2):148-156.

4 FDA'S ASSESSMENT OF NEED FOR A REMS

The REMS proposed by the sponsor addresses the risks of hepatotoxicity and teratogenicity.

Teratogenicity. Nonclinical reproductive and developmental toxicity data raises the concern that lomitapide may increase the risk of teratogenicity in humans. Treatment with lomitapide is long-term, thus increasing the probability of fetal exposure during critical periods of prenatal development. Lomitapide's clinical development program demonstrated the efficacy of this drug for the treatment of HoFH, a life-threatening disease. If approved, lomitapide will be used in a small at risk patient population managed primarily by healthcare providers experienced in the treatment of lipid disorders and in prescribing statins, which have a similar reproductive toxicity profile. Thus, for these reasons and based on FDA's regulatory precedent of managing most drugs with teratogenic risk with labeling only, DRISK recommends managing lomitapide's potential risk of teratogenicity through labeling only. Expansion of the indication and/or target patient and prescriber populations will require a reevaluation of the risk management approach.

Hepatotoxicity. Because of the potential risk of hepatotoxicity, lomitapide could not be approved without the necessary safeguards to restrict prescribing to certified prescribers who understand that lomitapide must be used only for treating patients in whom the benefit is thought to exceed this risk. Several factors support the implementation of a REMS for lomitapide to address the risk of potential hepatotoxicity. First, lomitapide is an effective therapy for HoFH. The clinical development program demonstrated lomitapide's efficacy in the reduction of LDL-C in the small HoFH patient population for whom there is an unmet need for effective therapies. Second, lomitapide is an NME for which the serious risk of hepatotoxicity is not fully characterized yet, given its unknown potential for progression of non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) is unknown. Third, patients with HoFH would require life-long exposure to this drug, which will likely increase a patient's risk of hepatotoxicity requiring ongoing monitoring for evidence of hepatic injury. Fourth, the expected prescriber population requires training in the appropriate patient selection for treatment with lomitapide and in the monitoring and management of the risk of hepatotoxicity. A REMS program would provide an opportunity to train all prescribers regarding the appropriate use and risks associated to the use of lomitapide regardless of their medical training background. Fifth, a REMS program could help minimize use of lomitapide outside of the approved indication.

FDA has used various approaches to manage the risk of hepatotoxicity for other approved products including labeling alone (e.g., felbamate, zileuton, tolcapone, trovafloxacin, propylthiouracil) and the implementation of REMS with a CP (fingolimod, tocilizumab, dronedarone) and ETASUs (bosentan, ambrisentan). The REMS for fingolimod, tocilizumab, and dronedarone used the CP to address multiple risks. There are no REMS programs addressing hepatic steatosis and no other approved product used in the treatment of dyslipidemias has a REMS. The particular circumstances associated to lomitapide are not common to other products with a risk of hepatotoxicity with the exception of mipomersen, an NME currently undergoing FDA review.

In summary, the available evidence of lomitapide's potential risk of hepatotoxicity and the anticipated context for use in clinical practice supports the implementation of a REMS to communicate current knowledge about the serious risk of hepatotoxicity, the need for monitoring and managing increased transaminases and hepatic steatosis, and the importance of prescribing this product for the approved indication.

5 SPONSOR'S REVISED REMS PROPOSAL

In a teleconference on August 27, 2012, FDA communicated to Aegerion its perspective and recommendations regarding a REMS for lomitapide. Subsequently, Aegerion included in their Advisory Committee meeting background document and slide presentation a REMS proposal that is similar to that recommended by FDA. Following is a description of the REMS proposal presented by the sponsor at the Advisory Committee meeting.

5.1 REVISED GOALS

- Risk Mitigation
  - To educate prescribers about
    - The approved indication for use of lomitapide
    - The risk of hepatic effects
    - The need to monitor patients during treatment as per product labeling
  - Limit access to patients in whom therapy with lomitapide is medically appropriate
- Risk Assessment
  - To evaluate long-term safety and effectiveness of risk mitigation measures through an observational cohort study

5.2 REVISED REMS ELEMENTS

- Specially certify and enroll prescribers
  - Have been trained on the educational materials
  - Understand the indication for lomitapide – prescriber attests to understand indication of use and certifies appropriateness of therapy for the patient
  - Understand the risks associated with lomitapide including hepatic effects and teratogenicity
  - Acknowledge the need to monitor hepatic transaminases during treatment – attests to obtaining aminotransferase levels in accordance with prescribing information
  - Agree to counsel the patient on the risks of lomitapide and instruct the patient to read the Medication Guide carefully
- Control and limit distribution via a single specialty pharmacy
- Ensure dispensing only to patients with a prescription from and enrolled prescriber and documentation of safe-use conditions

5.3 REVISED REMS ASSESSMENT

The proposed REMS assessment measures include enhanced pharmacovigilance, audits of the specialty pharmacy, prescriber surveys, and an observational study to document patient characteristics and frequency of monitoring.

The proposed observational study is a global cohort study including a minimum of 300 patients followed for five years. The outcomes of interest are the long-term safety profile of lomitapide, patterns of use, and long-term effectiveness in controlling serum lipid levels. A draft protocol of this study was included in the sponsor's original NDA submission and was reviewed by the Division of Epidemiology.[3]

6 ADVISORY COMMITTEE PANEL RECOMMENDATIONS

On October 17, 2012, the Endocrinologic and Metabolic Drugs Advisory Committee voted 13:2 in favor of the approval of lomitapide for the treatment of adult patients with HoFH. The panel recommended the REMS program restrict the drug to the approved indication. Some panel members additionally recommended a more rigorous postmarketing observational study to collect long-term safety data than that originally proposed by the sponsor.

7 FDA'S PROPOSED REMS

The following minimum strategy would provide a mechanism to support prescribers in the safe use of lomitapide in the targeted HoFH population, while deterring its use in the larger population of patients with hypercholesterolemia from the unknown consequences of drug-induced hepatic steatosis with chronic use of lomitapide.

7.1 GOALS

We are proposing that the REMS have the following goals:

- To educate prescribers about the approved indication for use of lomitapide, the potential risk of hepatotoxicity associated with the use of lomitapide, and the need to monitor patients during treatment with lomitapide as per product labeling
- To limit access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH.

Rationale for the proposed goals: The uncertainties regarding the clinical implications of increases in transaminases and steatosis of the liver preclude the formulation of a clear message for patients. Consequently, the proposed goal focuses on prescriber education only. The key actions required from a REMS to maintain the risk:benefit balance for lomitapide are to educate prescribers about the serious risk of hepatotoxicity, the need for monitoring increased transaminases and hepatic steatosis, and the importance of prescribing this product for the approved indication.

Requiring a laboratory diagnosis of HoFH for all patients in order to receive lomitapide is problematic for the following reasons:

- Genetic testing may not be available to all patients

- All genetic mutations defining HoFH are not known
- Commercial tests are not available for all genetic mutations

The proposed goals are measurable through the monitoring of prescriber and pharmacy certification statistics; the distribution of letters to prescribers, pharmacists, and professional societies; and via prescriber knowledge surveys.

7.2 REMS ELEMENTS

We propose the following components for the REMS.

- Elements to assure safe use to include:
    a. Health care professionals (HCP) who prescribe lomitapide are specially certified
    b. Pharmacies that dispense lomitapide are specially certified
    c. Lomitapide will be dispensed to patients with evidence or other documentation of safe-use conditions
- An implementation system
- A timetable for submission of assessments

7.2.1 ELEMENTS TO ASSURE SAFE USE

Healthcare providers who prescribe lomitapide will be specially certified

- Prescriber Certification (ETASU A) – Certification consists of training and program enrollment. Certification will be linked to ability to prescribe.

  Rationale: Mandatory Prescriber Certification (ETASU A) including prescriber training and enrollment is required to ensure that prescribers are aware of the potential risks associated with lomitapide, appropriate patient selection, and recommended monitoring parameters and clinical management. DRISK agrees in principle with the sponsor's proposal for prescriber certification. However, prescriber training should not be limited to reviewing the product label, Medication Guide, and Prescriber's Guide – as proposed by the sponsor – but will require a more formal approach such as a computer-based training module including knowledge verification questions at the end of each training module. The sponsor's proposed prescriber enrollment form has an acceptable format although the final text included will be revised once the Agency and the sponsor reach consensus on the key elements of this REMS.

  The prescriber enrollment form must include prescriber demographics, contact information, identifiers (e.g., National Provider Identification (NPI) number), and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS Program requirements.

  The requirement for prescriber certification will likely limit the number of healthcare providers able to prescribe lomitapide since many prescribers do not treat patients with HoFH and are therefore not likely to enroll in the program. It is unclear to what

extent this will result in a limitation of access to some patients who are candidates for therapy.

- Communications to certified prescribers (ETASU A) – all communications including letters addressed to healthcare providers and professional societies will be distributed as stipulated under ETASU A. A REMS website will be developed and maintained by the sponsor.

  Rationale: Ongoing REMS-related communications in support of prescriber certification will be part of ETASU A. The sponsor proposed a Communication Plan as a separate element of the REMS; however, DRISK deemed appropriate including all communications under the corresponding ETASU (i.e., ETASU A-prescriber certification or ETASU B- pharmacy certification). This alternative simplifies the REMS Program by keeping the elements of the REMS to a functional minimum while still allowing the implementation of ongoing communications between prescribers participating in the REMS and the REMS Program Coordinating Center.

  DRISK has no conclusive evidence of the effectiveness of the implementation of a communication system as described above but presumes that making this information accessible to prescribers will increase the probability of informing them about the risks associated to lomitapide, appropriate use of this product, and about REMS Program requirements.

Lomitapide will only be dispensed by pharmacies that are specially certified

- Pharmacy Certification (ETASU B) – Pharmacy certification will assure that lomitapide is dispensed only when prescribed by certified prescribers and after documentation of safe use conditions. Certification will be linked to ability to purchase and dispense lomitapide.

  Rationale – Pharmacy certification is required to ensure that a prescription for lomitapide is dispensed only when the prescriber is certified and has provided documentation of safe use conditions. See rationale for Prescriber Certification above and a description of safe use conditions in the next section below.

  The pharmacy certification process must include training of pharmacy representative regarding the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS Program requirements. The pharmacy enrollment form must include pharmacy/pharmacy representative contact information and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS Program requirements. Certified pharmacies would need to have systems in place to verify that only certified prescribers prescribe lomitapide to patients in whom therapy with lomitapide is medically appropriate. The certified pharmacies would not need to obtain additional documentation in support of the patient's medical need for the drug other than the prescriber attestation in the authorization form, nor would they need to ensure that the appropriate laboratory testing has been performed prior to dispensing lomitapide.

  The sponsor included in their original proposal a distribution system consistent with the REMS concept of pharmacy certification.

A requirement for pharmacy certification may restrict the number of pharmacies able to dispense lomitapide. It is unclear at this time whether the pharmacies that the sponsor intends to certify will make the lomitapide available to all US patients who are appropriate for treatment.

- Communications to certified pharmacies (ETASU B) – all communications including letters addressed to pharmacies or pharmacy representatives will be distributed as stipulated under ETASU B. A REMS website will be developed and maintained by the sponsor.

  Rationale – Ongoing REMS-related communications in support of pharmacy certification will be part of ETASU B. The sponsor proposed a Communication Plan as a separate element of the REMS; however, DRISK deemed appropriate including all communications under the corresponding ETASU (i.e., ETASU A-prescriber certification or ETASU B- pharmacy certification). This alternative simplifies the REMS Program by keeping the elements of the REMS to a functional minimum while still allows the implementation of ongoing communications between prescribers and pharmacies participating in the REMS and the REMS Program Coordinating Center.

Lomitapide will be dispensed only to patients with evidence or other documentation of safe-use conditions

- Safe use conditions – The proposed safe use condition consists of a "Prescription Authorization" form integrated with each new prescription (not refills) that will include the following statements attesting to the safe and appropriate use of lomitapide[4]:
  - I understand that TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).
  - I certify that this patient has a clinical or laboratory diagnosis consistent with HoFH.
  - I understand that lomitapide has not been studied in pediatric patients less than 18 years.
  - I attest that I have obtained the liver-related laboratory tests for this patient as directed in TRADENAME's prescribing information.
  - (b) (4)

[4] The statements of medical necessity are draft as of the date of this review and were based upon discussion within between DMEP and DRISK following the Endocrinologic and Metabolic Advisory Committee meeting on October 17, 2012.

The patient would not need to sign the form. The frequency of required documentation of safe use conditions will require further discussion within the Agency.

Rationale: This requirement for documentation of safe use conditions is included in FDA's proposal in support of the second REMS goal, "To limit access to therapy with lomitapide to patients in whom therapy with lomitapide is medically appropriate". This additional step, required before a prescription is dispensed, ensures that the prescriber will consider whether the use of lomitapide is appropriate therapy for each patient and avoids the need to keep long-term records of authorized patients because the authorization is built into each prescription.

(b) (4)

7.2.2 IMPLEMENTATION SYSTEM

At a minimum, the Implementation System must include the following elements:

1. a mechanism to train and certify prescribers and pharmacists,
2. a database of all enrolled prescribers and pharmacies,
3. a mechanism to ensure that lomitapide is distributed only to certified pharmacies,
4. audits of dispensing data to ensure that lomitapide is only being dispensed to patients who are prescribed lomitapide by certified prescribers,
5. a lomitapide REMS Program Coordinating Center to support, prescribers, pharmacies, and patients participating in the REMS Program,
6. a system to monitor and audit certified pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the REMS.

DRISK concurs in principle with the sponsor's proposed Implementation System for a REMS because it already includes the key implementation elements listed above.

7.2.3 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

6 months and 12 months after approval and annually thereafter.

DRISK concurs with the sponsor's proposal and recommend REMS assessment submissions at 6 months and 12 months after approval and annually thereafter.

7.3 REMS ASSESSMENT PLAN

The REMS Assessment Plan must include, at a minimum, the following elements:

1. REMS Program implementation metrics,
2. prescriber and pharmacy certification statistics,
3. documentation of prescriber and pharmacist awareness of the REMS materials and knowledge of REMS Program requirements,
4. documentation of compliance with REMS Program requirements,
5. analyses of drug utilization data, and
6. analyses of adverse event reports received during the assessment period and cumulatively, in particular, reports of liver toxicity.

DRISK concurs in principle with the sponsor's proposed REMS assessment plan.

7.4 REMS ELEMENTS PROPOSED BY THE SPONSOR BUT EXCLUDED BY FDA

Medication Guide

DRISK propose a Medication Guide be distributed outside of the REMS Program.

Rationale: There are several important product messages that must be conveyed to patients receiving treatment with lomitapide. These include the potential risk of hepatotoxicity and the need for monitoring transaminases and liver fat content; the potential for teratogenicity; the need to consume a low fat diet supplemented by fat-soluble vitamins and essential fatty acids; and the risk of potential dug-drug interactions.

The REMS Program centers on the potential risk of hepatotoxicity and on prescriber education given that, this risk is not fully characterized. FDA is not including as a component of the REMS patient education and understanding of the complex issues of non-alcoholic fatty liver disease and the concern about possible progression to non-alcoholic steatohepatitis (NASH) and therefore the Medication Guide is not a necessary element of the REMS.

Communication Plan

DRISK did not include a Communication Plan as an element of the REMS.

Rationale: As an alternative to a Communication Plan, DRISK proposes including all REMS-related communications in support of prescriber and pharmacy certification be part of ETASU A or ETASU B respectively. This alternative simplifies the REMS Program by keeping the elements of the REMS to a functional minimum while still allows the implementation of ongoing communications between prescribers and pharmacies participating in the REMS and the REMS Program Coordinating Center.

8 DISCUSSION

FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a REMS for lomitapide, DRISK balanced the demonstrated benefits of lomitapide in reducing LDL-C in the HoFH patient population and the potential risk of liver toxicity. The REMS proposed by FDA would support appropriate use of lomitapide, allowing it to be approved for use in the targeted patient population while protecting the larger hypercholesterolemic patient population by limiting prescribing of lomitapide to certified prescribers and dispensing to certified pharmacies. Certified pharmacies would dispense lomitapide only if the prescriber is certified and if the prescriber authorizes each prescription by attesting to understand the approved indication and that treatment with lomitapide is appropriate for the patient. In response to the Advisory Committee panel recommendations to strengthen the proposed REMS program, DRISK modified the REMS goals to restrict the use of lomitapide only to patients whose prescribers certify to have a clinical or laboratory diagnosis consistent with HoFH. The prescriber attestation statement included as part of the prescription authorization form will also reflect these changes to the goals.

DRISK considers that addition to the proposed REMS of safe use conditions linking dispensing of the drug to documentation of specific laboratory or imaging parameters is unwarranted at this time given the lack of evidence-based guidelines for their interpretation and may result in limitation of access to the drug. Until further clinical data is available, the management of HoFH patients treated with lomitapide will rely on the prescriber's clinical judgment.

The potential risk of teratogenicity identified in nonclinical studies is similar to that of the statins and can be managed in the HoFH population through labeling only. However, expansion of the indication and/or target patient and prescriber populations will require a reevaluation of the risk management approach.

Additional safety data required to characterize further lomitapide's safety profile will be collected through a postmarketing observational study and enhanced pharmacovigilance.

9 CONCLUSIONS

HoFH is a life-threatening disease for which there is a medical need for additional effective therapies. Lomitapide demonstrated to be effective in lowering LDL-C in patients with HoFH. Because of the potential risk of hepatotoxicity, lomitapide cannot be approved without the necessary safeguards to restrict prescribing to certified prescribers who understand that lomitapide must be used only for treating patients in whom the benefit is thought to exceed this risk. DRISK recommends a REMS with prescriber certification, pharmacy certification, and documentation of safe use conditions as described above to ensure that the benefits of lomitapide outweigh the potential risk of serious liver toxicity.

The potential risk of teratogenicity should be managed with labeling only, however, DRISK will have a low threshold for the implementation of additional risk measures if new safety data demonstrate changes in lomitapide's risk:benefit profile (e.g., expansion of the indication and/or the at risk patient population).

10 RECOMMENDATIONS FOR DMEP

DRISK recommends DMEP request the sponsor to submit a modified REMS proposal as described in section 11 below.

11 COMMENTS FOR THE SPONSOR

Please submit a revised REMS proposal including the following goals and elements:

1. Goals

- To educate prescribers about the approved indication for use of lomitapide, the potential risk of hepatotoxicity associated with the use of lomitapide, and the need to monitor patients during treatment with lomitapide as per product labeling
- To limit access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH

2. REMS Elements

1. Elements to assure safe use to include:
    a. Health care professionals (HCP) who prescribe lomitapide are specially certified (ETASU A) – including mandatory prescriber certification consisting

of prescriber training and enrollment. FDA agrees in principle with the sponsor's proposal for prescriber certification, however, prescriber training should not be limited to reviewing the product label, Medication Guide, and Prescriber's Guide but will require a more formal approach such as a computer-based training module including knowledge verification questions at the end of each training module.

The prescriber enrollment form must include prescriber demographics, contact information, identifiers (e.g., National Provider Identification (NPI) number), and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements.

Communications to certified prescribers, including letters addressed to healthcare providers and professional societies, will be distributed as stipulated under ETASU A. The sponsor should develop and maintain a REMS website. A document with suggested revisions to the healthcare provider and professional society letters is appended. Please note that the objective of this document is to provide guidance; the text included in the final version of this document must be consistent with the approved label.

b. Pharmacies that dispense lomitapide are specially certified (ETASU B) – pharmacy certification will assure that lomitapide is dispensed only when prescribed by certified prescribers and after documentation of safe use conditions. Certification will be linked to ability to purchase and dispense lomitapide. The pharmacy certification process must include training of pharmacy representative regarding the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements. The pharmacy enrollment form must include pharmacy/pharmacy representative contact information and a section to attest understanding of the approved indication and appropriate use of lomitapide, the risks associated with its use, and REMS program requirements.

   Communications to certified pharmacies, including letters addressed to pharmacies or pharmacy representatives, will be distributed as stipulated under ETASU B.

c. Lomitapide will be dispensed to patients with evidence or other documentation of safe-use conditions (ETASU D) – The proposed safe use condition consists of a "Prescription Authorization" form integrated with each new prescription that will include the following statements attesting to the safe and appropriate use of lomitapide:

   - I understand that TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and non-high-density

lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

- I certify that this patient has a clinical or laboratory diagnosis consistent with HoFH.
- I understand that lomitapide has not been studied in pediatric patients less than 18 years.
- I attest that I have obtained the liver-related laboratory tests for this patient as directed in TRADENAME's prescribing information.
- (b) (4)

An example of the Prescription Authorization form is appended.

2. An implementation system – at a minimum, the Implementation System must include the following elements:
   - a mechanism to train and certify prescribers and pharmacists
   - a database of all enrolled prescribers and pharmacies
   - a mechanism to ensure that lomitapide is distributed only to certified pharmacies
   - audits of dispensing data to ensure that lomitapide is only being dispensed to patients who are prescribed lomitapide by certified prescribers
   - a lomitapide REMS Program Coordinating Center to support, prescribers, pharmacies, and patients participating in the REMS Program
   - a system to monitor and audit certified pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the REMS

3. A timetable for submission of assessments – 6 months and 12 months after approval and annually thereafter.

3. REMS Supporting Document

   a. The REMS Supporting Document must be consistent with all changes made to the REMS document.

   b. REMS Assessment Plan - include, at a minimum, the following elements:
      - prescriber and pharmacy certification statistics
      - documentation of prescriber and pharmacist awareness of the REMS materials and knowledge of REMS program requirements

- analyses of drug utilization data, and analyses of adverse event reports received during the assessment period and cumulatively, in particular, reports of liver toxicity

4. General Comments

- Resubmission Requirements and Instructions: Submit the revised proposed REMS for lomitapide with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.
- Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

ATTACHMENTS

- **PROPOSED LOMITAPIDE REMS PRESCRIPTION AUTHORIZATION FORM**
- **EXAMPLES OF REVISED DEAR HEALTHCARE PROVIDER /PROFESSIONAL ASSOCIATION LETTERS**

8 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

AMARILYS VEGA
11/08/2012

CLAUDIA B MANZO
11/08/2012
concur