CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	December 21, 2012
From	Christine P. Nguyen, MD Acting Deputy Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	203-858
Applicant Name	Aegerion Pharmaceuticals, Inc.
Date of Submission	2/29/12
PDUFA Goal Date	12/29/12
Proprietary Name / Established (USAN) Name	Juxtapid/lomitapide
Dosage Forms / Strength	5, 10, 20 mg oral capsules (immediate release) Recommended starting dose of 5 mg daily at bedtime. After 2 weeks the daily 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.
Proposed Indication	An adjunct to a low-fat diet and other lipid-lowering 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)
Regulatory Action:	Approval

Material Reviewed/Consulted Reviews from the following disciplines:	**Names of discipline reviewers**
Clinical	James Smith/ Eric Colman
Statistics	Cynthia Liu/ Jon Todd Sahlroot
Pharmacology Toxicology	Brian (Tim) Hummer/ Karen Davis-Bruno
CMC Biopharmaceutics	Xavier Ysern/ Ali H Al Hakim Elsbeth Chikhale/ John Duan
Clinical Pharmacology	Sze (Johnny) Lau/ Immo Zadezensky
Office of Scientific Investigations	Susan Leibenhaut/ Janice Pohlman
OSE/DEPI	Patricia Bright/ Diane Wysowski
OSE/DRISK	Amarilys Vega/ Cynthia LaCivita
Pediatric and Maternal Health Staff	Jeanine Best/ Melissa Tassinari

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction and Background

This memo summarizes the basis for the regulatory action for lomitapide. This oral drug is being proposed for the orphan indication of the treatment of homozygous familial hypercholesteremia (HoFH). In-depth review and analyses of specific issues can be found in the primary reviews of the respective disciplines. This memo contains my summary, assessments, and conclusions concerning the major issues identified during the review of this application.

Lomitapide is a first-in-class small molecule inhibitor of the microsomal triglyceride protein (MTP) that transfers lipids to apolipoprotein B to form the apo B-containing lipoprotein complex. Inhibition of MTP prevents the assembly and secretion of apo B-containing lipoproteins, which include VLDL-C (the precursor of LDL-C), and chylomicrons from the liver and intestine, respectively.

Homozygous familial hypercholesteremia (HoFH) results from loss of function mutations in both alleles of the LDL receptor (LDL-R). These mutations render the LDL-Rs absent or non-functional leading to reduced clearance of LDL particles from circulation, resulting in marked elevation in plasma LDL-C levels. Untreated LDL-C levels in individuals with HoFH usually range from 500 to 1000 mg/dL. If left untreated, HoFH patients die prematurely from accelerated atherosclerotic cardiovascular disease by the second or third decade of life. In the U.S., the prevalence of HoFH is approximately 1 per million persons.

Treatment options for HoFH are limited in number and in scope. High potency HMG-CoA reductase inhibitors (statins), with or without a cholesterol absorption inhibitor, and LDL apheresis are the mainstay of therapy (see Table 1). Statin therapy depends on functional LDL-Rs for most of its lipid lowering effects and, therefore, has limited efficacy in HoFH. Similar to dialysis, LDL apheresis is an extracorporal procedure that selectively removes apo-B containing lipoproteins (VLDL-C, LDL-C, lipoprotein (a), and triglycerides). The procedure, however, needs to be performed on a chronic, repetitive basis of every one to two weeks, and there are currently only 35 apheresis centers in the U.S. Liver transplantation has been employed rarely as a last resort.

Table 1: Non-surgical therapies for HoFH

Therapy	Mechanism of action	LDC-C lowering response in HoFH
HMG-CoA reductase inhibitors	LDLR activity	< 10 – 25%
Cholesterol absorption inhibitors	LDLR activity, inhibits cholesterol absorption	< 10%
LDL-apheresis*	LDL-C removal	~30 – 40%[1]

*Response based on time averaged LDL-C levels; acutely, apheresis lowers LDL-C by 50-75%

Drug therapy in combination with LDL apheresis can typically reduce LDL-C by 45% to 55%.[2] Because HoFH patients have such elevated LDL-C levels at baseline (> 500 mg/dL),

[1] Pfohl M, Naoumova RP, Klass C, Knisel W, Jakober B, Risler T, Thompson GR. Acute and chronic effects on cholesterol biosynthesis of LDL-apheresis with or without concomitant HMG-CoA reductase inhibitor therapy. J Lipid Res. 1994;35(11):1946.
[2] Gilbert R. Thompson, M. Barbir, D. Davies, et al. Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis 208 (2010) 317–321.

combining multiple treatment modalities still fails to provide adequate control of LDL-C, and HoFH patients remain at high-risk for serious adverse cardiovascular events and premature death. There is a clear need for additional therapies to help HoFH patients either approach or reach LDL-C treatment goals.

This NDA submission supports the use of lomitapide at a starting daily dose of 5 mg titrated to a maximum of 60 mg, based on safety and tolerability, as an adjunct to diet and lipid lowering therapies to reduce LDL-C in HoFH patients.

2. Recommendations of Review Disciplines regarding Approvability

This section summarizes key recommendations from the review disciplines.

CMC: In his review signed on October 18, 2012, the primary reviewer (Xavier Ysern) recommended approval of lomitapide from a CMC perspective.

Biopharmaceutics (ONDQA): In her review signed October 26, 2012, the primary reviewer (Elsbeth Chikhale) recommended approval of lomitapide from a biopharmaceutics perspective. A waiver for the requirement to conduct a BA/BE study for the 10 mg capsule strength was granted.

Pharmacology Toxicology: In his review signed November 5, 2012, the primary reviewer (Brian [Tim] Hummer) recommended approval of lomitapide from a pharmacology-toxicology perspective. Safety concerns based on preclinical findings are discussed in Section 4 (Safety). The team recommended a juvenile toxicology study, as a postmarket requirement, to be conducted prior to evaluating lomitapide in pediatric HoFH patients.

Clinical Pharmacology: In his review signed November 5, 2012, the primary reviewer (Sze [Johnny] Lau) recommended approval from a clinical pharmacology perspective. Recommended dosing modifications based on drug-drug interactions, food effect, and hepatic/renal impairment that will be incorporated into labeling are discussed in Section 4 (Safety).

Statistics: In her review signed November 30, 2012, the primary reviewer (Cynthia Liu) concluded that lomitapide was effective in reducing LDL-C and the pre-specified secondary lipid parameters and recommended approval from a statistical perspective.

Clinical: In his review signed November 27, 2012, the primary reviewer (James Smith) recommended approval from a clinical perspective. Important clinical findings and assessments are discussed in Sections 3 (Efficacy) and 4 (Safety) below.

I concur with the recommendation of approval from the review disciplines.

3. Efficacy

Efficacy of lomitapide in HoFH patients was demonstrated in one Phase 3 trial (HoFH-pivotal, 29 HoFH patients); with supportive evidence from one Phase 2 study (HoFH-pilot, 6 HoFH

patients). The primary efficacy endpoint in both trials was the percent change from baseline to endpoint in directly measured serum LDL-C; each subject served as his or her own control.

The surrogate endpoint of serum LDL-C has been an accepted primary efficacy measure in marketing applications for lipid-lowering therapies in the U.S. The relationship between reductions in LDL-C levels and decreased risk of adverse cardiovascular outcomes has been well established for statin therapy. Although there are no data correlating LDL-C reduction and improved cardiovascular outcomes for MTP inhibitors, there is no reason to believe that LDL-C would not be an acceptable efficacy endpoint for HoFH patients treated with lomitapide. Moreover, a definitive cardiovascular outcomes trial in HoFH patients would be infeasible because of the rarity of the disease, and LDL-C is the most appropriate surrogate measure available.

The HoFH-pivotal trial was a multinational, open-label, single-arm trial in 29 HoFH patients on stable diet and maximally tolerated LDL lowering drugs, with or without apheresis, at baseline. Patients received lomitapide as add-on therapy at an individually defined maximum tolerated dose between 5 and 60 mg once daily for 78 weeks (weeks 0 to 26 was the efficacy phase, weeks 26 to 78 was the safety phase). Patients could enroll in the extension study (HoFH-extension) after completing the 78 weeks of treatment; the extension study is ongoing.

The primary efficacy endpoint, % change in LDL-C levels from baseline to Week 26/end of treatment, was analyzed using paired t-test performed on the intent to treat population (all 29 patients) with last-observation-carried-forward (LOCF) imputation of missing data. Primary efficacy results are shown in Table 2. It should be noted that the observed LDL-C reduction from lomitapide treatment was in addition to the lipid lowering effects of baseline therapies.

Table 2: Primary Endpoint – Percent change in LDL-C from baseline to Week 26 (HoFH-pivotal)

N = 29	Baseline LDL-C (mg/dL)	Week 26/ITT/LOCF LDL-C (mg/dL)	Absolute Change from Baseline (mg/dL)	Relative Change from Baseline (%)	P*
Mean (SD) 95% CI Median Min, Max	337 (114) 357 152, 565	191 (107) 169 28, 443	-147 (127) -107 -351, +49	**-40** (32) -52 to -27 **-50** -93, +21	<0.001

Source: Adapted from primary statistical review (Cynthia Liu), Table 2
* P-value based on paired t-test for mean % change

Maximum LDL-C reduction reached plateau at Week 18 and was maintained at approximately 45% reduction at Week 56; the mean maximum tolerated dose at Week 26 and at Week 56 was approximately 40 mg.

Categorical LDL-C response: 19 of the 29 patients (66%) had LDL-C reductions ≥ 25%, with 8 (28%) having LDL-C levels < 100 mg/dL. Four of these 8 patients were receiving apheresis. The fact that HoFH patients treated with adjunctive lomitapide could attain the National Cholesterol Education Program's target LDL-C treatment goal is noteworthy.

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