CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

CHEMISTRY REVIEW(S)

NDA 203-858

(Lomitapide mesylate) Capsules

Aegerion Pharmaceuticals

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 203-585

2. REVIEW #: 3

3. REVIEW DATE: 03-Dec-2012

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	29-Feb-2012
Amendment Request for Proprietary Name Review (b) (4)	01-Mar-2012
Amendment Request for Proprietary Name Review (b) (4)	30-May-2012
Amendment Response to 08-May-2012 Quality Information Request *Seq. 0012*	19-Jun-2012
Amendment Response to 27-Jun-2012 Quality Information Request *Seq. 0015*	02-Jul-2012
Amendment Response to 27-Jun-2012 Quality Information Request (2, 6 & 7) *Seq. 0018*	23-Jul-2012
Amendment Request for Proprietary Name Review (b) (4) *Seq. 0021*	08-Aug-2012
Amendment Response to 19-Jul-2012 Quality Information Request *Seq. 0023*	31-Aug-2012
Amendment Response to 06-Sep-2012 Quality Information Request *Seq. 0028*	28-Sep-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Amendment Request for Proprietary Name Review (Juxtapid™) *Seq. 0032*	27-Nov-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Aegerion Pharmaceuticals
Address:	101 Main St., Suite 1850 Cambridge, MA 02142
Representative:	Martha J.Carter Chief Regulatory Officer and Senior Vice President
Telephone:	617-500-7795

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) (proposed tradenames)
(b) (4) *not acceptable* (29-May-2012)
(b) (4) (03-Aug-2012)
(b) (4) (*not acceptable*)
Juxtapid™ (under review)

b) Non-Proprietary Name (USAN): Lomitapide Mesylate

c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 1-New Molecular Entity
- Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
Orphan Drug (Designation request 07-2459, granted for treatment of homozygous familial hypercholesterolemia on 23-Oct-2007)

10. PHARMACOL. CATEGORY: Microsomal triglyceride transfer protein (MTP) inhibitor. Lipid altering agent.
[Indication: Treat homozygous familial hypercholesterolemia (HoFH) as an adjunct to diet and other lipid-lowering treatments.]

11. DOSAGE FORM: [Hard Gelatin] Capsules

12. STRENGTH/POTENCY: 5, 10, and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

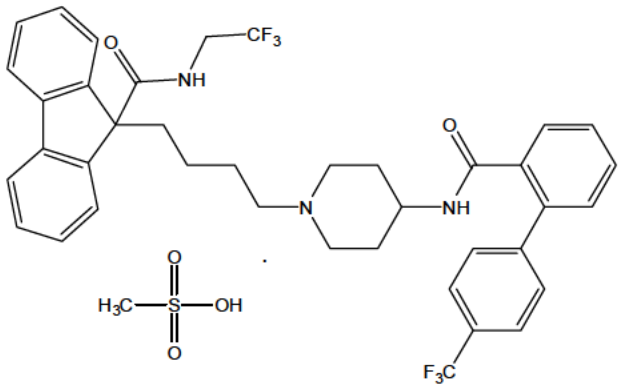
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lomitapide Mesylate

Chemical Structure:



Molecular Formula: $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$

Molecular Weight: 789.8 amu (693.7 + 96.1)

Chemical Name:

N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide, methanesulfonate salt

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	LOA date
[redacted]	[redacted]	[redacted] (b) (4)	4	Adequate		18-Jan-2012
			4	Adequate		08-Feb-2012
			4	Adequate		08-Feb-2012
			4	Adequate		16-Dec-2011

[1] Action codes for DMF Table:
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	50,820	Lomitapide Mesylate Capsules
IND	77,775	AEGR-733(Formerly BMS-201038)

18. STATUS:

ONQA:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	02-Dec-2012	Office of Compliance
Pharm/Tox	Acceptable		
Biopharm	Acceptable	26-Oct-2012	Dr. Elsbeth Chikhale
DMEPA	Proposed proprietary tradenames [redacted] (b) (4) and Juxtapid™ under review		
Methods Validation	Revalidation by Agency laboratories is not recommended		
OPDRA			
EA	Acceptable		Part of CMC review # 1
Microbiology	N.A.		

Executive Summary Section

The Chemistry Review for NDA 203-858

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC point of view this application is recommended for APPROVAL. All pending issues have been satisfactorily resolved.

Based on the stability data submitted, an expiry of 24 months for drug product (b) (4) packaged in (b) (4) high-density polyethylene (HDPE) bottles sealed with an induction seal and closed with a (b) (4) child resistant (CR) twist-off closure is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug Substance Lomitapide Mesylate

Lomitapide mesylate drug substance is a white to off-white powder. It is very soluble in methanol, acetone, and ethanol. Solubility is reduced in other common solvents and it is insoluble in heptane. Aqueous solubility is greatest at approximately pH 3.5-4 with a solubility limit of 3.7 mg/mL. It is moderately hygroscopic, the maximum water adsorption is approximately 5 % at 95 % relative humidity (RH).

(b) (4)

Lomitapide mesylate is synthesized using a (b) (4) . The (b) (4) key starting materials, (b) (4) are commercially available. The intended commercial batch size for lomitapide is (b) (4)

BMS, the original manufacturer, had identified 5 related impurities and 1 degradant that could be present in the lomitapide drug substance. Of these 5, only 2, (b) (4) have been observed in lomitapide drug substance produced at (b) (4) (commercial manufacturer). The highest levels observed in (b) (4) manufactured drug batches have been approximately (b) (4) and approximately (b) (4) . These 2 impurities have been qualified to levels (b) (4) and are limited to (b) (4) in the drug substance specifications. (b) (4) This degradant has

not been qualified but is limited by specification to [redacted] in accordance with the thresholds described in ICH Q3A given a maximum daily dose of ≤ 2 g/day.

Drug substance specifications include description (visual), identification (HPLC and IR), assay (HPLC), purity (HPLC), residue on ignition (sulfated ash content), [redacted], residual solvents (GC), starting materials [redacted], heavy metals (USP<231>) [redacted], particle size distribution, physical form (XRPD), water content [redacted] and microbial testing (total aerobic microbial count, total yeast and mould count, and tests for specific microorganisms). The total amount of impurities cannot exceed [redacted].

The acceptance criterion for the physical form is "XRPD pattern corresponds to [redacted]

[redacted]

· Drug Product

The formulation and manufacturing process for lomitapide capsules was developed by Bristol-Myers Squibb (BMS), the company that initially developed lomitapide. The qualitative composition of the formulation has not changed during the course of development and the quantitative composition has changed only to accommodate changes in the strength of the dose. Three strengths, 5 mg, 10 mg and 20 mg, are proposed for commercialization. Different strength capsules, all Size 1 hard gelatin capsule, are distinguished by the color of the capsule and the imprinting.

The manufacturing process for the production of lomitapide drug product consists of [redacted]

XRPD analyses of drug product have shown that, [redacted]

[1] A drug is considered highly soluble when the highest dose strength (HDS) is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5 *(Biopharmaceutics Classification System)*. The HDS value for lomitapide is 20 mg, and the solubility of either Form of lomitapide for that range of pH is higher than 0.08 mg/mL (20/250 mg/mL).

Proposed drug product specifications include Description (visual), Identification (HPLC and MS), Assay (HPLC), Purity (HPLC), Dissolution (Apparatus 2), Dosage Uniformity (USP<905>), (b) (4) and Microbial testing (USP<61> and <62>). The same HPLC method, method QM3255, employed for both assay and impurity determinations in the drug substance, is used for the drug product. The purity acceptance criteria requires that the (b) (4) Impurity to be (b) (4) any unidentified impurity (b) (4) and the total impurities not to exceed (b) (4)

The stability of lomitapide drug product has been established by placing 3 primary lots of 5 mg capsules and 4 primary lots of 20 mg capsules into long-term and accelerated stability studies. The proposed commercial drug product configuration will differ from the primary stability lots in capsule color (removal of a colorant in the case of the 20 mg capsule drug product) and the addition of imprinting on the capsule for identification. To bridge these differences between the primary stability lots and proposed commercial configuration a comparison stability study was carried out. The results of the 3-month bridging stability study are comparable to the results for the primary stability lots and indicate that the changes have had no impact on the stability of lomitapide drug product.

The stability of the 10 mg strength for lomitapide drug product, is bracketed by the data from the 5 mg and 20 mg primary stability lots. Based on the 24-month stability results at 25 °C/60 % RH for the 5 mg and 20 mg lomitapide capsule drug product, the Applicant proposes a 24-month expiry dating for the 5, 10, and 20 mg commercial drug product. The stability data fully supports the proposed 24-months expiry dating.

B. Description of How the Drug Product is Intended to be Used

Lomitapide Capsules are 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. The drug product is intended to be administered orally once daily at bedtime, with a glass of water and without food.

Prior to initiating treatment the patients should follow a low-fat diet supplying less than 20 % of energy from fat, and should continue this diet during treatment. 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.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live.

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD	Chemist, ONDQA/ DNDQA III/ Branch VII	Date: 03-De-2012

B. Endorsement Block

Ali Al-Hakim, PhD	Branch Chief, ONDQA/ DNDQA III/ Branch VII	Date: 03-Dec-2012

C. CC Block

Kati Johnson Regulatory PM/ODEII/DMEP

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/s/

XAVIER J YSERN
12/03/2012

ALI H AL HAKIM
12/03/2012

NDA 203-858

(Lomitapide mesylate) Capsules

Aegerion Pharmaceuticals

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 203-585

2. REVIEW #: 2

3. REVIEW DATE: 17-Oct-2012

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
--	--

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-Feb-2012
Amendment Request for Proprietary Name Review [redacted]	01-Mar-2012
Amendment Request for Proprietary Name Review [redacted]	30-May-2012
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted] (proposed tradenames)
[redacted] *not acceptable* (29-May-2012)
[redacted] *not acceptable*, [redacted] (03-Aug-2012)
[redacted] (under review)

b) Non-Proprietary Name (USAN): Lomitapide Mesylate

c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 1-New Molecular Entity
- Submission Priority: Standard

Chemistry Review Data Sheet

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[Indication: Treat homozygous familial hypercholesterolemia (HoFH) as an adjunct to diet and other lipid-lowering treatments.]

11. DOSAGE FORM: [Hard Gelatin] Capsules

12. STRENGTH/POTENCY: 5, 10, and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

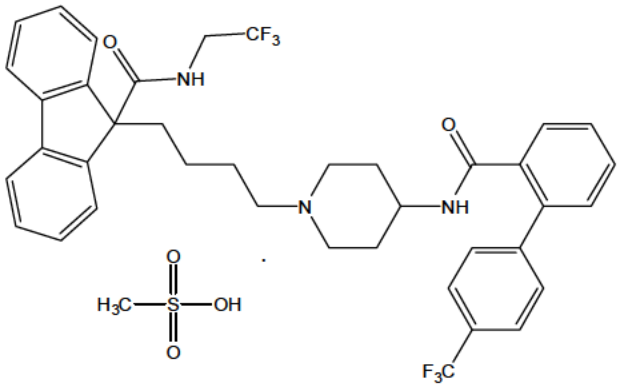
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lomitapide Mesylate

Chemical Structure:



Molecular Formula: $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$

Molecular Weight: 789.8 amu (693.7 + 96.1)

Chemical Name:

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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	LOA date
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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IND	77,775	AEGR-733(Formerly BMS-201038)

18. STATUS:

ONDC:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Pending	17-Oct-2012	
Pharm/Tox	--		
Biopharm	Dissolution acceptance criterion modified		Dr. Elsbeth Chikhale
DMEPA	Proposed proprietary tradename (b) (4) under review		
Methods Validation	Revalidation by Agency laboratories is not recommended		
OPDRA			
EA	Acceptable		Part of this review
Microbiology	Pending		

Executive Summary Section

The Chemistry Review for NDA 203-858

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC point of view this application is recommended for APPROVAL. The recommendation from the Office is Compliance for the acceptability of the manufacturing sites is still pending.

Based on the stability data submitted, an expiry of 24 months for drug product (b) (4) packaged in (b) (4) high-density polyethylene (HDPE) bottles sealed with an induction seal and closed with a (b) (4) child resistant (CR) twist-off closure is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug Substance Lomitapide Mesylate

Lomitapide mesylate drug substance is a white to off-white powder. It is very soluble in methanol, acetone, and ethanol. Solubility is reduced in other common solvents and it is insoluble in heptane. Aqueous solubility is greatest at approximately pH 3.5-4 with a solubility limit of 3.7 mg/mL. It is moderately hygroscopic, the maximum water adsorption is approximately 5 % at 95 % relative humidity (RH).

(b) (4)

Lomitapide mesylate is synthesized using a (b) (4)

The (b) (4) key starting materials, (b) (4) are commercially available. The intended commercial batch size for lomitapide is (b) (4)

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not been qualified but is limited by specification to [redacted] (b) (4) in accordance with the thresholds described in ICH Q3A given a maximum daily dose of ≤ 2 g/day.

Drug substance specifications include description (visual), identification (HPLC and IR), assay (HPLC), purity (HPLC), residue on ignition (sulfated ash content), [redacted] (b) (4) residual solvents (GC), starting materials [redacted] (b) (4) heavy metals (USP<231> [redacted] (b) (4), particle size distribution, physical form (XRPD), water content [redacted] (b) (4) and microbial testing (total aerobic microbial count, total yeast and mould count, and tests for specific microorganisms). The total amount of impurities cannot exceed [redacted] (b) (4)

The acceptance criterion for the physical form is "XRPD pattern corresponds to [redacted] (b) (4)

[redacted] (b) (4)

· Drug Product

The formulation and manufacturing process for lomitapide capsules was developed by Bristol-Myers Squibb (BMS), the company that initially developed lomitapide. The qualitative composition of the formulation has not changed during the course of development and the quantitative composition has changed only to accommodate changes in the strength of the dose. Three strengths, 5 mg, 10 mg and 20 mg, are proposed for commercialization. Different strength capsules, all Size 1 hard gelatin capsule, are distinguished by the color of the capsule and the imprinting.

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XRPD analyses of drug product have shown that, [redacted] (b) (4)

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The stability of the 10 mg strength for lomitapide drug product, is bracketed by the data from the 5 mg and 20 mg primary stability lots. Based on the 24-month stability results at 25 °C/60 % RH for the 5 mg and 20 mg lomitapide capsule drug product, the Applicant proposes a 24-month expiry dating for the 5, 10, and 20 mg commercial drug product. The stability data fully supports the proposed 24-months expiry dating.

B. Description of How the Drug Product is Intended to be Used

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C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live.

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Xavier Ysern, PhD	Chemist, ONDQA/ DNDQA III/ Branch VII	Date: 17-Oct-2012

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Ali Al-Hakim, PhD	Branch Chief, ONDQA/ DNDQA III/ Branch VII	Date: 17-Oct-2012

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Kati Johnson	Regulatory PM/ODEII/DMEP

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/s/

XAVIER J YSERN
10/18/2012

ALI H AL HAKIM
10/18/2012

NDA 203-858

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Aegerion Pharmaceuticals

Xavier Ysern, PhD

ONDQA/ DNDQA III/ Branch VII

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Representative:	Martha J.Carter Chief Regulatory Officer and Senior Vice President
Telephone:	617-500-7795

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted] (b) (4) proposed tradenames)
[redacted] (b) (4) *not acceptable* (29-May-2012)
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- Submission Priority: Standard

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Chemistry Review Data Sheet

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11. DOSAGE FORM: [Hard Gelatin] Capsules

12. STRENGTH/POTENCY: 5, 10, and 20 mg

13. ROUTE OF ADMINISTRATION: Oral

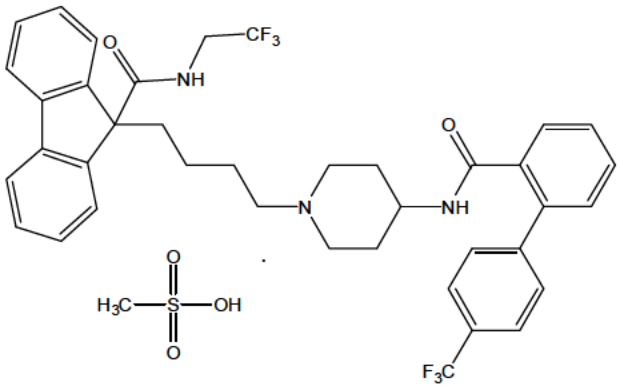
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Lomitapide Mesylate

Chemical Structure:



Molecular Formula: $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$

Molecular Weight: 789.8 amu (693.7 + 96.1)

Chemical Name:

N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide, methanesulfonate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	LOA date
(b) (4)			4	Adequate		18-Jan-2012
			4	Adequate		08-Feb-2012
			4	Adequate		08-Feb-2012
			4	Adequate		16-Dec-2011

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	50,820	Lomitapide Mesylate Capsules
IND	77,775	AEGR-733(Formerly BMS-201038)

18. STATUS:

ONDC:

CONSULTS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N.A.		
EES	Pending		
Pharm/Tox	--		
Biopharm	Pending		
DMEPA	Proposed proprietary tradenames have been not accepted		
Methods Validation	Revalidation by Agency laboratories is not recommended		
OPDRA			
EA	Acceptable		Part of this review
Microbiology	Pending		

Executive Summary Section

The Chemistry Review for NDA 203-858

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC point of view this application is recommended for APPROVAL pending, (1) completion of the submission of the Method Validation Package and (2) satisfactory recommendation of the dissolution specification by the Biopharm review team. The recommendation from the Office is Compliance for the acceptability of the manufacturing sites is still pending.

Based on the stability data submitted, an expiry of 24 months for drug product (b) (4) packaged in (b) (4) high-density polyethylene (HDPE) bottles sealed with an induction seal and closed with a (b) (4) child resistant (CR) twist-off closure is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug Substance Lomitapide Mesylate

Lomitapide mesylate drug substance is a white to off-white powder. It is very soluble in methanol, acetone, and ethanol. Solubility is reduced in other common solvents and it is insoluble in heptane. Aqueous solubility is greatest at approximately pH 3.5-4 with a solubility limit of 3.7 mg/mL. It is moderately hygroscopic, the maximum water adsorption is approximately 5 % at 95 % relative humidity (RH).

(b) (4)

Lomitapide mesylate is synthesized using a (b) (4)

The (b) (4) key starting materials, (b) (4) are commercially available. The intended commercial batch size for lomitapide is (b) (4)

BMS, the original manufacturer, had identified 5 related impurities and 1 degradant that could be present in the lomitapide drug substance. Of these 5, only 2, (b) (4), have been observed in lomitapide drug substance produced at (b) (4) (commercial manufacturer). The highest levels observed in (b) (4) manufactured drug batches have been approximately (b) (4) and approximately (b) (4)

(b) (4) These 2 impurities have been qualified to levels (b) (4) and are limited to (b) (4) in the drug substance specifications. (b) (4) This degradant has not been qualified but is limited by specification to (b) (4) in accordance with the thresholds described in ICH Q3A given a maximum daily dose of ≤ 2 g/day.

Drug substance specifications include description (visual), identification (HPLC and IR), assay (HPLC), purity (HPLC), residue on ignition (sulfated ash content), (b) (4) residual solvents (GC), starting materials (b) (4) heavy metals (USP<231> (b) (4), particle size distribution, physical form (XRPD), water content (b) (4) and microbial testing (total aerobic microbial count, total yeast and mould count, and tests for specific microorganisms). The total amount of impurities cannot exceed (b) (4)

The acceptance criterion for the physical form is "XRPD pattern corresponds to (b) (4)

(b) (4)

· Drug Product

The formulation and manufacturing process for lomitapide capsules was developed by Bristol-Myers Squibb (BMS), the company that initially developed lomitapide. The qualitative composition of the formulation has not changed during the course of development and the quantitative composition has changed only to accommodate changes in the strength of the dose. Three strengths, 5 mg, 10 mg and 20 mg, are proposed for commercialization. Different strength capsules, all Size 1 hard gelatin capsule, are distinguished by the color of the capsule and the imprinting.

The manufacturing process for the production of lomitapide drug product consists of (b) (4)

XRPD analyses of drug product have shown that, (b) (4)

[1] A drug is considered highly soluble when the highest dose strength (HDS) is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5 *(Biopharmaceutics Classification System)*. The HDS value for lomitapide is 20 mg, and the solubility of either Form of lomitapide for that range of pH is higher than 0.08 mg/mL (20/250 mg/mL).

(b) (4)

Proposed drug product specifications include Description (visual), Identification (HPLC and MS), Assay (HPLC), Purity (HPLC), Dissolution (Apparatus 2), Dosage Uniformity (USP<905>), (b) (4), and Microbial testing (USP<61> and <62>). The same HPLC method, method QM3255, employed for both assay and impurity determinations in the drug substance, is used for the drug product. The purity acceptance criteria requires that the (b) (4) Impurity to be (b) (4) any unidentified impurity (b) (4) and the total impurities not to exceed (b) (4)

The stability of lomitapide drug product has been established by placing 3 primary lots of 5 mg capsules and 4 primary lots of 20 mg capsules into long-term and accelerated stability studies. The proposed commercial drug product configuration will differ from the primary stability lots in capsule color (removal of a colorant in the case of the 20 mg capsule drug product) and the addition of imprinting on the capsule for identification. To bridge these differences between the primary stability lots and proposed commercial configuration a comparison stability study was carried out. The results of the 3-month bridging stability study are comparable to the results for the primary stability lots and indicate that the changes have had no impact on the stability of lomitapide drug product.

The stability of the 10 mg strength for lomitapide drug product, is bracketed by the data from the 5 mg and 20 mg primary stability lots. Based on the 24-month stability results at 25 °C/60 % RH for the 5 mg and 20 mg lomitapide capsule drug product, the Applicant proposes a 24-month expiry dating for the 5, 10, and 20 mg commercial drug product. The stability data fully supports the proposed 24-months expiry dating.

B. Description of How the Drug Product is Intended to be Used

Lomitapide Capsules are 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. The drug product is intended to be administered orally once daily at bedtime, with a glass of water and without food.

Prior to initiating treatment the patients should follow a low-fat diet supplying less than 20 % of energy from fat, and should continue this diet during treatment. 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.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live.

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Chemist, ONDQA/ DNDQA III/ Branch VII Date: 21-Sep-2012

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief, ONDQA/ DNDQA III/ Branch VII Date: 21-Sep-2012

C. CC Block

128 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

XAVIER J YSERN
09/21/2012

ALI H AL HAKIM
09/21/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	203-858
Submission Date	2/29/12
Product name, generic name of the active	Lomitapide
Dosage form and strength	Capsules – 5mg/capsule, 10 mg/capsule and 20 mg/capsule
Applicant	Aegerion Pharmaceuticals Inc.
Clinical Division	Division of Metabolic and Endocrine Product
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Supervisory Lead	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?	x		
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x	x	Applicant mentioned that lomitapide is BCS class 1, however, supportive data as per BCS Guidance were not provided
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in *vivo* BA or BE information in the submission?	x		

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		The applicant should be asked to provide: (b) (4) [redacted]

{See appended electronic signature page}
Elsbeth Chikhale, Ph.D. 5/6/12
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D. 5/6/12
Biopharmaceutics Supervisory Lead (acting) Date
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
05/06/2012

ANGELICA DORANTES
05/06/2012

ONDQA Initial Quality Assessment (IQA) and Filing Review
NDA 203858 (lomitapide)

NDA	**203858**
Applicant:	**Aegerion Pharmaceuticals Inc.**
Stamp Date:	**29-FEB-2012**
PDUFA Date:	**29-DEC-2012**
Established Name:	**lomitapide**
Proposed Proprietary Name:	**[none indicated]**
Dosage form and strength:	**Capsule 5 mg, 10 mg, and 20 mg**
Route of Administration:	**Oral**
Indications:	**Homozygous familial hypercholesterolemia**

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

CMC Lead: Su (Suong) Tran

Is the Product Quality Section of the application fileable from a CMC perspective?	
Yes	No
☒	☐

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
☒	☐	1. (b) (4) [redacted] 2.

RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)				16-Dec-2012	
				18-Jan-2012	
				08-Feb-2012	
				08-Feb-2012	

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☒	
EES	☒	☐	EER submitted to OMPQ on 06-FEB-2012
Pharm/Tox	☒	☐	Evaluation of the genotoxicity potential of identified impurities and degradants.
Methods Validation	☐	☐	*Validation may be requested of FDA labs after test methods are finalized.*
EA	☐	☒	*The categorical exclusion claim will be assessed by Primary Reviewer.*
New Drug Micro	☐	☒	
CDRH	☐	☒	
Other	☐	☐	

c. Other Applications or Submissions to note (if any):
IND 50820 and IND 77775

d. Previous Communications with the Applicant to note (if any):

Major issues discussed at the ONDQA Pre-NDA meeting on 05-APR-2011 include:

- FDA agreed that the proposed characterization studies are sufficient.
- (b) (4) are not acceptable starting materials because they (b) (4).
- The sponsor would provide in the NDA pharmaceutical development data to justify the selected particle size distribution for the drug substance.
- FDA agreed that the NDA can include stability data from only one batch of drug substance for filing.
- FDA reminded the sponsor that per GRMPs, a complete NDA should be submitted and additional unsolicited amendments may not be reviewed.
- Stability data from one batch of the 10 mg strength would be included in the NDA along with manufacturing details.

- Stability data required in the NDA should be at least 6-month long term and accelerated for at least one registration batch for each of the 5 mg and 20 mg strengths.
- FDA agreed that the stability protocol is acceptable.
- FDA agreed that the first two registration batches of the 5 mg and 10 mg would be within 1/10 of the commercial scale and the third batch of each strength would be a validation batch.

Major issues discussed at the OND Pre-NDA meeting on 05-JUL-2011 include:

- The sponsor agreed to submit the NDA with 3-month stability from 3 registration batches of each dosage strength and up to 2-year data from clinical batches. The clinical and registration batches differ in printing and batch size. Both products will have the same capsule size 1 and same container closure systems.

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	☐	☒	
Combination Products	☐	☒	
Nanotechnology	☐	☒	
PET	☐	☒	
QbD Elements	☐	☒	
SPOTS	☐	☒	

Is a team review recommended?

Yes	No	Suggested expertise for team
☐	☒	

CMC Summary and Critical Issues

This is an electronic NDA, filed as a 505(b)(1) application.

The drug substance lomitapide mesylate is a small synthetic New Molecular Entity. It is an inhibitor of the microsomal triglyceride transfer protein.

The drug product is 5 mg, 10 mg, or 20 mg (lomitapide, free-base) immediate release capsule. The excipients are pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silicon dioxide and magnesium stearate. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide. The imprinting ink contains shellac, black iron oxide and propylene glycol.

The product will be packaged in 28-count (b) (4) bottles with child-resistant closures for storage at room temperature.

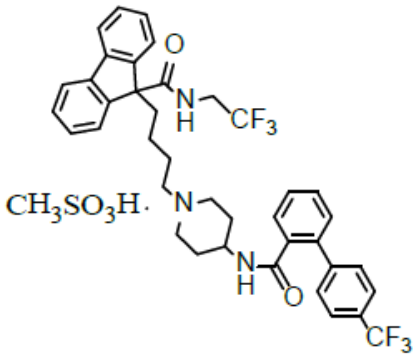
Maximum daily dose is 60 mg.

Drug substance:

USAN:	lomitapide mesylate
Other names:	AEGR-733 BMS-201038 BMS-201038-04
Chemical name (IUPAC):	methanesulfonic acid; N-(2,2,2-trifluoroethyl)-9-[4-[4-[[2-[4-(trifluoromethyl)phenyl] benzoyl]amino]piperidin-1-yl]butyl]fluorene-9-carboxamide
Chemical Abstracts Service (CAS) Registry number:	202914-84-9

The structure of lomitapide mesylate is illustrated in Figure 1. It does not contain any chiral centres.

Figure 1: Chemical Structure of Lomitapide Mesylate



Lomitapide drug substance is a white to off-white powder. It is very soluble in methanol, acetone, and ethanol. Solubility is reduced in other common solvents and it is insoluble in heptane. Aqueous solubility is greatest at approximately pH 3.5-4 with a solubility limit of 3.7 mg/mL.

Manufacturing process. The applicant states that the (b) (4) starting materials, (b) (4) are commercially available and includes the names of the suppliers in the NDA. The reviewer will determine whether these compounds are acceptable as starting materials based on all available information in the NDA, especially information on processes that can remove/reduce carry-over impurities from these compounds to the final drug substance. It is not clear whether these compounds are the same as proposed at the Pre-NDA meeting because the code numbers/names of the compounds are not the same, and there is no CMC review of the Pre-NDA meeting

package. The manufacturing process consists of (b) (4)

Figure 2: Lomitapide Chemical Synthesis Flowchart

(b) (4)

Comparability of the product used in the clinical studies, stability studies, and commercial product. The development of lomitapide was conducted by Bristol-Myers Squibb (BMS), including Phase 1 and 2 studies. The drug was transferred to Aegerion in 2007 who conducted the phase 3 study. The applicant

states that the drug substance manufacture remains the same during the transfer from BMS to the applicant. However, differences in (b) (4) and particle size distributions were found across all drug substance batches (as summarized below).

(b) (4)

ND: not done
[1] Test performed in 2011-2012
[2] Not observable at release

The drug substance exists (b) (4) have different melting points, dissolution rates, and solubility. (b) (4)

(b) (4)

74-day comment to the applicant: You have not provided adequate information to show whether the (b) (4) *would affect the product safety or efficacy. Propose and justify acceptance criteria for* (b) (4) *in the drug substance specification. In addition, justify* (b) (4) *in the product stability specification given that the limited data in the NDA show* (b) (4) *during the drug product manufacture.*

The particle size distribution was found to affect dissolution rates and absorption in a dog PK study (b) (4) . The reviewer will confirm that the proposed acceptance criteria for particle size distribution are appropriate for the commercial product based on the data of the clinical batches.

Structural characterization. The structure of lomitapide was analyzed by elemental analysis, FT-IR, 1H and 13C NMR.

Specification. The drug substance specification is copied here.

Table 1: Testing and Specifications for the Lomitapide Drug Substance

TEST	TEST METHOD	SPECIFICATION
Description (visual)[a]	100.01	(b) (4)
Identification (HPLC)	1713.01	
Identification (FT-IR)	100.06 (Ref A1713)	
Assay (HPLC)[a]	1713.01	
Individual identified impurities (HPLC)[a] (b) (4)	1713.01	
Individual unidentified impurities (HPLC)[a]	1713.01	
Total impurities (HPLC)[a]	1713.01	
Residue on ignition (ROI) Sulphated ash content	100.41 (Harmonised USP <281> Ph.Eur. 2.4.14)	
(b) (4)	1713.05	
Residual solvents (GC)		
(b) (4)	1713.02	
	1713.02	

TEST	TEST METHOD	SPECIFICATION
(b) (4)		(b) (4)
Starting materials		
(b) (4)	1713.06	
	1713.02	
Heavy metals	100.73 (USP <231>) Method II	
(b) (4)	100.74 (USP <730>)	
Particle size	100.72	
Physical form (XRD)[a]	100.70	
Water determination[a]	1713.07	
Microbiological examination of non-sterile products[a]		
Microbial enumeration test: Total aerobic microbial count (TAMC)	100.22 (Harmonised USP <61> Ph.Eur. 2.6.12)	
Microbial enumeration test: Total yeast & mould count (TYMC)	100.22 (Harmonised USP <61> Ph.Eur. 2.6.12)	
Tests for specified microorganisms	100.22 (Harmonised USP <62> Ph.Eur. 2.6.13)	

[a] Indicates tests that will be conducted as part of formal stability and/or retest programs.
[b] "Corrected" purity = (current assigned "as-is" purity) × (previous assigned "corrected" purity) (previous assigned "as-is" purity)

Impurities. The drug substance includes limits on two process impurities (b) (4), one degradan (b) (4), and one (b) (4). The applicant states that the (b) (4), it is only a theoretical impurity based on the synthetic scheme, and it has not been found in the drug substance. The reviewer will determine if the available release and stability data support the proposed limits. The reviewer will confirm with the PharmTox team tha (b) (4) are adequately qualified because the proposed limit is (b) (4) for each (ICH qualification threshold = 0.15%), and for the (b) (4), that its limit of (b) (4) is below the threshold of toxicological concern for the maximum daily dose of 60 mg. The degradant (b) (4) has an acceptable limit of (b) (4) per ICH qualification.

(b) (4)

Stability. As previously agreed by FDA on 05-APR-2011, the NDA includes long-term stability data (49-month) for only one batch of drug substance, batch 1713-1713-07-001, and very limited data (3-month and 1-month) for two additional batches. The applicant found (b) (4) and a (b) (4) degradant in the data of batch 1713-1713-07-001 (see copied table on the next page) but attributed this increase to inadequate packaging of the stability sample itself. The applicant claims that the actual packaging of the bulk drug substance is better at (b) (4) However, there is no information to support the claim. The bulk drug substance is stored in (b) (4) The stability sample is stored in (b) (4) . The stability sample packaging (b) (4) and since the NDA includes very limited

stability data, the applicant's requested retest date of (b) (4) at 25 °C/60% RH is not acceptable. The (b) (4) result at Month 3 for the second stability batch (1713-1713-11-001H) shows the same increasing trend observed at Month 4 for the first stability batch (1713-1713-07-001). The reviewer will consider all available data and determine an appropriate retest date. It should be noted that the (b) (4) degradant (b) (4) reaches the maximum limit of (b) (4) at Month 12, (b) (4)

Table 11: Summary of Impurity Data Up to 36 Months from the Stability Study of Lomitapide Drug Substance, (b) (4) Batch 1713-1713-07-001

TEST	INITIAL (T0)	STORAGE CONDITIONS	1M	4M	6M	12M	24M	36M
(b) (4)		25°C/60% RH						(b) (4)
		40°C/75% RH						
		25°C/60% RH						
		40°C/75% RH						

[a] Impurities >0.10% only are reported. Data is not shown for 2 other impurities observe, (b) (4) (b) (4) These 2 impurities were present at T0 and did not show any trending when compared to initial T0 testing.

74-day comment to the applicant: It is not clear whether (b) (4) in the drug substance is caused by the packaging of the stability sample itself or the packaging of the bulk drug substance used for long-term storage. You claim that this issue only pertains to batch 1713-1713-07-001 because the packaging of the stability sample of this batch (b) (4) result at Month 3 for the second stability batch (1713-1713-11-001H) shows the same increasing trend observed at Month 4 for batch 1713-1713-07-001. Therefore, your requested retest date of (b) (4) at room temperature is unrealistic.

Drug product

5 mg capsules: Orange/orange hard gelatin capsule printed with black ink "A733" and "5 mg"
10 mg capsules: Orange/white hard gelatin capsule printed with black ink "A733" and "10 mg"
20 mg capsules: White/white hard gelatin capsule printed with black ink "A733" and "20 mg"
Composition is copied here.

Table 2: Components and Composition of Lomitapide Capsules, 5 mg, 10 mg, and 20 mg

COMPONENT	FUNCTION	SPECIFICATION	AMOUNT 5 MG CAPSULE	%*	AMOUNT 10 MG CAPSULE	%*	AMOUNT 20 MG CAPSULE	%*
(b) (4)								
Lomitapide mesylate[a]	Active Ingredient	In-house	5.69 mg (5.00 mg free base)	5.69	11.39 mg (10.00 mg free base)	5.69	22.77 mg (20.00 mg free base)	11.39
Pregelatinized Starch	(b) (4)	NF, Ph.Eur.	(b) (4)					
Microcrystalline Cellulose		NF, Ph.Eur.						
Lactose Monohydrate[b]		NF, Ph.Eur.						
Sodium Starch Glycolate		NF, Ph.Eur.						
(b) (4)								(b) (4)
Colloidal Silicon Dioxide (b) (4)	(b) (4)	USP, Ph.Eur						(b) (4)
Magnesium Stearate		NF, Ph.Eur.						
Sodium Starch Glycolate		NF, Ph.Eur.						
Total Amount			100 mg	100	200 mg	100	200 mg	100
(b) (4)								

Established name and dosage strength. The proposed established name of the product is "lomitapide", which is acceptable because it correlates with the dosage strength of the free base, as per current CDER policy on nomenclature. The reviewer will ensure that the full amount of the salt is included in the prescribing information and packaging labels, but it should not have the same prominence as the dosage strength.

Comparability of the product used in the clinical studies, stability studies, and commercial product. The primary stability batches were used in the phase 3 clinical studies (except for the 10 mg strength which was not used in any clinical study). The biowaiver request for the 10 mg strength will be evaluated by the Biopharm team.

The applicant states that the clinical/stability batches and the commercial product only differ in the imprinting ink and color (see copied summary below). The 5 mg and 10 mg are (b) (4)

(b) (4), 100 mg fill weight for the 5 mg strength and 200 mg fill weight for the 10 mg strength. The 20 mg strength is (b) (4) to the other strengths. Stability batches include three primary batches (also clinical batches) for each of the 5 mg and 20 mg strengths, and one commercial batch for each of the 5 mg, 10 mg, and 20 mg strengths.

Table 1: Comparison of Clinical Drug Product to Proposed Commercial Drug Product

	CLINICAL DRUG PRODUCT	PROPOSED LAUNCH DRUG PRODUCT
Capsule Size 5 mg 10 mg 20 mg	 Size 1 Not Applicable Size 1	 Same Size 1 Same
Capsule Color 5 mg 10 mg 20 mg	 Swedish orange[1] body & cap Not Applicable Swedish orange body & cap	 Same White[2] body & Swedish orange cap White body & cap
Capsule Imprint	None	Edible black ink
Batch Size 5 mg 10 mg 20 mg	(b) (4)	
Container/closure System	(b) (4) HDPE bottle with induction seal and closure	Same
Bottle Count 5 mg 10 mg 20 mg	 25 and 35 Not Applicable 35, 65 and 100	 28 28 28

[1] (b) (4) red iron oxide + (b) (4) titanium dioxide
[2] titanium dioxide

All the drug product batches/lots are summarized below:

Table 1: Lomitapide Drug Product Lots

STRENGTH	USE	LOT NO.	SCALE (CAPSULES)	PROCESS	MFG DATE
2.5 mg capsules	Clinical Ph. 2 and Stability	L0105924	(b) (4)		3/2007
2.5 mg capsules	Clinical Ph. 2 and Stability	L0108400			8/2007
5 mg capsules	Clinical Ph. 2 and Stability	L0105923			3/2007
5 mg capsules	Clinical Ph. 2 and Stability	L0108401			8/2007
5 mg capsules	Clinical Ph. and Stability	L0109391			12/2007
5 mg capsules	Clinical Ph. 3 and Stability	L0206440			2/2009
5 mg capsules	Clinical Ph. 1, 2, 3 and Stability	L0302138			6/2010
5 mg capsules	Bridging	L0306297			8/2011
10 mg capsules	Bridging	L0306298			8/2011
20 mg capsules	Clinical Ph. 3 and Stability	L0109390			12/2007
20 mg capsules	Clinical Ph. 3 and Stability	L0203329			5/2008
20 mg capsules	Clinical Ph. 3 and Stability	L0206441			2/2009
20 mg capsules	Clinical Ph. 3 and Stability	L0302139			6/2010
20 mg capsules	Bridging	L0306299			8/2011

Excipients. All excipients are USP/NF grade. (b) (4) and BSE/TSE certification statements are included in the NDA.

Manufacturing process of the drug product. The manufacturing process of the drug product is the

(b) (4)

Drug product specification.

The drug product specification is copied here.

Table 3: Release Specifications for Commercial Lots of Lomitapide 5 mg, 10 mg and 20 mg Capsules

TEST	TEST METHOD	5 MG, 10 MG AND 20 MG CAPSULES
Description (visual)[a]	QM0028	**5 mg capsule:** Size 1 hard gelatine capsule with Swedish orange body and Swedish orange cap imprinted with "5 mg" on body and "A733" on cap, containing a white to off-white powder **10 mg capsule:** Size 1 hard gelatine capsule with White body and Swedish orange cap imprinted with "10 mg" on body and "A733" on cap, containing a white to off-white powder **20 mg capsule:** Size 1 hard gelatine capsule with White body and White cap imprinted with "20 mg" on body and "A733" on cap, containing a white to off-white powder
Identification I (HPLC)	QM3255	(b) (4)
Identification II (MS)	QM4432	
Assay (HPLC)[a]	QM3255	
Individual identified impurities (HPLC)[a] (b) (4)	QM3255	
Individual unidentified impurities (HPLC)[a]	QM3255	
Total impurities (HPLC)[a]	QM3255	
Dissolution (Apparatus 2)[a]	QM3216 Harmonised USP<711> Ph.Eur. 2.9.3	
Uniformity of dosage units (HPLC)	QM3255 Harmonised USP <905> Ph.Eur. 2.9.40	
(b) (4)		

Microbiological examination of nonsterile product[a]		
Microbial enumeration test: total aerobic microbial count (TMAC)	QM4418 Harmonised USP <61> Ph.Eur. 2.6.12	(b) (4)
Microbial enumeration test: total yeast and mould count (TYMC)	QM4418 Harmonised USP <61> Ph.Eur. 2.6.12	
Test for specified microorganisms	QM4418 Harmonised USP <62> Ph.Eur. 2.6.13	

[a] Indicates tests that will be conducted on stability.

- **Limits on degradation products.** The applicant states that no degradation product has been found above the ICH reporting threshold of 0.10%. The theoretical (b) (4) degradant at (b) (4) (discussed in the drug substance section earlier in this review) has a limit of (b) (4) which meets the ICH identification threshold for the maximum daily dose of 60 mg (and below the ICH qualification threshold of 0.5%). The reviewer will determine whether the degradant control is adequate based on all available stability data.

  It is noted that while the drug substance is hygroscopic, the known (b) (4) degradant at (b) (4) (discussed in the drug substance section earlier in this review) has not been found in the drug product. The labeling includes a statement that the product should be protected from moisture. The container closure (b) (4). The drug substance specification has (b) (4) to minimize degradation, while the drug product specification has (b) (4) based on the lack of degradation so far in the stability studies.

- **Dissolution.** All dissolution-related information (including data, test method, and acceptance criteria) will be reviewed by the Biopharm team.

- (b) (4) **and microbial limits**. If needed, the reviewer may have an informal consult with the Microbiology team to discuss the (b) (4) potential for microbial growth. Since the product is a solid oral dosage form, per current ONDQA's policy, no formal consult request is sent to Microbiology.

Container closure systems for product distribution.

Lomitapide 5, 10, and 20 mg capsules will each be supplied in (b) (4) high-density polyethylene (HDPE) bottles sealed with an induction seal and closed with a (b) (4) child resistant twist-off closure. Each bottle will contain 28 capsules. (b) (4)

(b) (4)

- **Safety of the packaging components**. The applicant states that the components (bottle, cotton, blister materials) comply with applicable indirect food additives regulations.
- **Suitability of the packaging components**. The primary stability batches were packaged in the proposed commercial container closure systems.
- **DMFs**. The primary reviewer will review information in the NDA and DMFs per internal policy on the review of container closure systems for solid oral drug products.

Stability of the drug product.

A sufficient amount of stability data is submitted for filing purposes as previously discussed with FDA at the 05-JUL-2011 Pre-NDA meeting. As agreed by FDA, stability data are provided for primary stability batches in the 5 mg and 20 mg strengths that were clinical batches and limited bridging data from the commercial product in all three dosage strengths. The reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.

Table 6: Lots Used for Stability Testing of Lomitapide 5, 10, and 20 mg Capsule Drug Product

PRODUCT	LOT NO.	LOT SIZE	CAPSULES PER CONTAINER	DATE OF MFG	MAXIMUM STUDY DURATION	AVAILABLE DATA
Primary Stability Lots		(b) (4)				
5 mg capsule	L0108401[a]		35 count	23 Aug 2007	24 mo.	24 mo.
	L0109391		25 count	13 Dec 2007	24 mo.	24 mo.
	L0206440		25 count	19 Feb 2009	36 mo.	24 mo.
	L0302138		35 count	14 Jun 2010	36 mo.	12 mo.
20 mg capsule	L0109390		65 count	18 Dec 2007	24 mo.	24 mo.
	L0109390		100 count	18 Dec 2007	24 mo.	24 mo.
	L0203329		35 count	19 May 2008	24 mo.	24 mo.
	L0206441		65 count	20 Feb 2009	24 mo.	24 mo.
	L0206441		100 count	20 Feb 2009	24 mo.	24 mo.
	L0302139		100 count	15 Jun 2010	36 mo.	12 mo.
Bridging Lots						
5 mg capsule	L0306297		14 count	17 Aug 2011	36 mo.	3 mo.
	L0306297		30 count	17 Aug 2011	36 mo.	3 mo.
10 mg capsule	L0306298		30 count	17 Aug 2011	36 mo.	1 mo.
20 mg capsule	L0306299		28 count	17 Aug 2011	36 mo.	3 mo.
	L0306299		90 count	17 Aug 2011	36 mo.	1 mo.

[a] Made with BMS drug substance

Facility

List of facilities included in EER:

Table 1: Manufacturing Sites for Commercial Lots of Lomitapide Drug Product

SITE	FUNCTIONS
(b) (4)	

Table 2: Testing Sites for Commercial Lots of Lomitapide Drug Product

SITE	FUNCTIONS
(b) (4)	

Table 3: Manufacturing Sites for Commercial Batches of Lomitapide Drug Substance

SITE	FUNCTIONS
(b) (4)	

Table 4: Testing Sites for Commercial Batches of Lomitapide Drug Substance

SITE	FUNCTIONS
(b) (4)	

All sites are inspection-ready.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
1.	Is the CMC section organized adequately?	☒	☐	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	☒	☐	☐	
3.	Are all the pages in the CMC section legible?	☒	☐	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☒	☐	☐	
B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	☐	
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	☒	
7	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	☐	
8	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	☐	

9	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	☐	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☐	☐	☒	*See table on cover page.*

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	☐	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☒	☐	☐	
15.	Does the section contain information on impurities?	☒	☐	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	☐	
17.	Does the section contain controls for the DS?	☒	☐	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	☐	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	☐	
21.	Does the section contain container and closure information?	☒	☐	☐	

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	☐	
23.	Does the section contain information on composition?	☒	☐	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	☐	
28.	Have any biowaiver been requested?	☒	☐	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	☐	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	☐	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
34.	Is there a methods validation package?	☒	☐	☐	
H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	☒	
I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	☐	
38.	Does section contain tradename and established name?	☒	☐	☐	
J. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	☒	☐	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	☒	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	☒	☐	☐	See first page.

This document will be signed in DARRTS by the following:

CMC Lead
Branch Chief

{See appended electronic signature page}

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

/s/

SUONG T TRAN
04/25/2012

ALI H AL HAKIM
04/25/2012