CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125390Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: 02/21/2014
To: Administrative File, STN 125390
From: Steven Fong, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D. Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Addendum to Microbiology Quality Review of Original BLA
US License: #1854
Applicant: Amylin Pharmaceuticals, LLC
Facility: (b) (4)
Product: Metreleptin
Dosage: (b) (4) mg/kg per daily dose
Indication: Treatment for diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy
Due date: PDUFA goal date: 2/24/2014

Recommendation on Approvability – The BLA, as amended, was reviewed from a microbiology quality perspective, and is recommended for approval. The current assessment provides an addendum to an initial Review submitted to DARRTS 11/26/2013. The addendum considers four Amendments, 125390/0.55, 125390/0.56, 125390/0.59, and 125390/0.60 that contained information regarding endotoxin detection, container closure integrity testing, stopper (b) (4), shipping validation, and stability testing. Two PMCs are listed at the end of the addendum.

The current assessment represents an addendum to an initial Microbiology Quality Review for STN 125390 submitted to DARRTS 11/26/2013. The initial Review did not include a concluding recommendation regarding BLA approvability because the following were not provided by the Sponsor prior to the GRMP review deadline:

- Endotoxin spiking and recovery data for undiluted Metreleptin DP to assess whether the DP inhibits endotoxin recovery.
- Data from studies to assess minimum leak size during performance of container closure integrity (CCI) validation assays.
- Issuance of a letter of authorization permitting Agency review of stopper (b) (4) information in DMF (b) (4)
- Data supporting hold periods for Metreleptin buffer and formulated Metreleptin DP.

- A more detailed description of the procedures and data for shipping validation, including the procedures for validating protection from temperature fluctuations.
- A post-approval commitment that includes the use of container closure integrity in lieu of sterility testing for product stability assessment, and performance of testing on commercial lots placed on stability.

The current addendum considers Amendments containing this information that were received 12/16/2013 (Amendment 125390/0.55); 12/27/2013 (Amendment 125390/0.56), and 1/21/2014 (Amendments 125390/0.59 and 125390/0.60). The responses are presented according to topic, with the relevant IR questions being indicated in italic font and the responses in regular font. For reference, a summary of all microbiology quality-related submissions for the BLA, including the submission numbers, sequences, and dates for Amendments, is presented below in Table 1. The table specifies the Amendments being considered in the current Addendum, and the IR questions that the Amendments are responding to.

TABLE 1. Summary of Submissions Considered in Current DP Microbiology Quality Review

Submission	Sequence Number	Submission Type	Submission Date	IR Being Responded To	Comments
125390/0.2	0003	Amendment	4/2/2012	N/A	Amendment containing CMC information.
125390/0.18	0017	Amendment	3/27/2013	N/A	Amendment containing updates to CMC information.
125390/0.36	0036	Amendment	10/07/2013	IR-1 submitted 9/16/2013	Response to IR-1 Questions 2, 3, 4, 11, 12, and 16.
125390/0.37	0037	Amendment	10/22/2013	IR-1 submitted 9/16/2013	Response to IR-1 Questions 1, 5, 6, 7, 8. 9. 10, 13, 14, and 15.
125390/0.55*	0055	Amendment	12/16/2013	IR-1 submitted 9/16/2013	Updated responses to IR-1 Questions 3 and 15. Initial responses were provided in Amendments 125390/0.36 and 125390/0.37.
125390/0.56*	0056	Amendment	12/27/2013	IR-3 submitted 12/03/2013	IR-3 was submitted after submission of Review 1, and contained questions Regarding CCI method sensitivity studies, a LOA for DMF (b) (4), shipping validation, and stability testing.
125390/0.59*	0059	Amendment	1/21/2014	IR-2 Question 1 submitted 11/12/2013	Amendment response to IR-2 received after submission of Review 1. IR-2 was submitted 11/9/2013 but wasn't recorded in DARRTS until 11/12/2013. Response contained data for LER issue.
125390/0.60*	0060	Amendment	1/21/2014	IR-4 submitted 1/9/2014	IR-4 requested a PMC for performance of CCI method sensitivity studies and clarification regarding shipping validation.

Amendments considered in current Review 2.

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/s/

STEVEN FONG
02/21/2014
Recommended for approval from a microbiology quality standpoint.

PATRICIA F HUGHES TROOST
02/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: 11/27/2013
To: Administrative File, STN 125390
From: Steven Fong, Ph.D., Reviewer, CDER/OC/OMPQ/DGMPA/BMAB
Endorsement: Patricia Hughes, Ph.D. Team Leader, CDER/OC/OMPQ/DGMPA/BMAB
Subject: Original BLA
US License: #1854
Applicant: Amylin Pharmaceuticals, LLC
Facility: (b) (4)
Product: Metreleptin
Dosage: (b) (4) mg/kg per daily dose
Indication: Treatment for diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy
Due date: PDUFA goal date: 2/24/2014

Recommendation on Approvability – The approvablity of the drug product portion of this application is pending until the following have been resolved. The Review will be amended when the additional information is provided.

- Endotoxin spiking and recovery data for undiluted drug product.
- Data from studies designed to assess the minimum detectable container closure leak size.
- Issuance of a letter of authorization permitting Agency review of DMF (b) (4)
- A more detailed description of the procedures and data for shipping validation, including the procedures for validating protection from temperature fluctuations, and data from studies to assess protection from physical damage.
- A post-approval commitment that includes the use of container closure integrity in lieu of sterility testing for product stability assessment, and performance of testing on commercial lots placed on stability.

Summary:

A. Brief Description of the Manufacturing Processes, including changes that relate to sterility assurance and product quality microbiology. The subject BLA provides information supporting licensure of the (b) (4), as a manufacturing site for Metreleptin DP. (b) (4)

(b) (4)

B. Brief Description of Deficiencies – See recommendation on approvability on Review Page 1.

C. Assessment of Risk Due to Deficiencies – Risk assessment cannot be made until the additional information indicated on Review Page 45 is provided.

Remarks

1) The contact person for this submission is:
   Sandra Matsumoto
   Manager, Regulatory Affairs
   Amylin Pharmaceuticals, Inc.
   9360 Towne Centre Drive
   San Diego, CA 92121
   Voice: 858-309-7424
   Fax: 858-625-0737

2) The subject BLA was received 12/15/2010 as a rolling submission. CMC information was provided in Amendment 125390/0.03 (sequence 0003) on 4/2/2012. IRs were sent to the Applicant on 9/16/2013 (IR-1), 11/08/2013 (IR-2), and 11/26/2013 (IR-3). The questions are listed at the end of this Review. The dates and sequence numbers for the Amendment responses are indicated in Review Table 1 (Review Page 3).

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/s/

STEVEN FONG

11/26/2013

Responses to information requests regarding microbiology quality were not received prior to Review submission. Approvability of the drug product portion of the application is pending until the requested information has been received and assessed.

PATRICIA F HUGHES TROOST

11/26/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Kalavati Suvarna, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA	125390/0
APPLICANT	Amylin Pharmaceuticals, LLC (a subsidiary of Bristol-Myers Squibb)
US LICENSE NUMBER	1854
SUBMISSION REVIEWED	Original BLA
PRODUCT	MYALEPT (Metreleptin) Other names: Recombinant-Methionyl Human Leptin (r-metHuLeptin); AC164594
MANUFACTURING FACILITY	Drug substance: Sandoz GmbH Biochemiestrasse 10, 6250 Kundl, Austria (FEI: 3002806523) (b) (4) [redacted]
INDICATION	Treatment of diabetes mellitus and/or hyperglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy
DOSAGE FORM	Lyophilized powder for subcutaneous injection (10 mg)
SUPPORTING DOCUMENTS	IND 50,259 and IND 101,824
CDER RECEIPT DATE	April 3, 2012
REVIEW ASSIGN DATE	April 4, 2012
REVIEW COMPLETE DATE	October 18, 2013
GRMP GOAL DATE	November 27, 2013
PDUFA GOAL DATE	February 24, 2014
PROJECT MANAGER	Patricia Madara
DIVISION	Division of Metabolism and Endocrinology Products
TO	S:\archive\BLA\125390\STN125390.rev.mem.BLA.10-18-2013.doc

1. PRODUCT QUALITY MICROBIOLOGY SUMMARY

I. EXECUTIVE SUMMARY

The subject of this BLA is metreleptin, a recombinant analog of human leptin, indicated for the treatment of diabetes mellitus and/or hypertriglyceridemia in an orphan population of pediatric and adult patients with inherited or acquired lipodystrophy. Metreleptin differs from the human leptin sequence by one additional amino acid (methionine) at the amino-terminal end. Human leptin is a hormone secreted by adipose tissues and plays an important role in fat and glucose metabolism, and regulation of energy homeostasis.

Metreleptin is a non-glycosylated 16 kDa protein hormone (147 amino acid) produced by recombinant technology in *E.coli*. The polypeptide contains one disulfide bond between Cys-97 and Cys-147. It is an acidic protein with pI of 6.2. The solubility of metreleptin at pH 4 is in excess of 70 mg/mL and at neutral pH is 2 mg/mL. Metreleptin self-associates to form soluble oligomers in aqueous solution. The drug substance is formulated at a final concentration of 20 mg/mL in (b) (4) glycine, (b) (4) sucrose, (b) (4) polysorbate 20, and (b) (4) glutamic acid, pH 4.25. The drug substance is (b) (4) The metreleptin drug substance is manufactured by Sandoz GmbH in Kundl, Austria. The site was inspected from August 16 - 24, 2012 and the inspection has been classified as VAI. Release and stability testing is conducted by Sandoz GmbH, Amylin Pharmaceuticals, Inc. (San Diego, California), (b) (4)

The proposed treatment regimen for MYALEPT (metreleptin for injection) is 0.02 mg/kg for patients ≤ 40 kg and 1.25 to 2.5 mg for patients >40 kg administered subcutaneously once daily.

This review covers microbial control of the drug substance manufacturing process described in the original BLA and amendments [eCTD sequences 0003 dated 4/2/2012 (CMC section), 0004 dated 4/10/2012 (Trade name) 0005 dated 4/13/2012 (manufacturing schedule), 0009 dated 7/19/2012 (information request dated 27 June 2012), 0013 dated 9/17/2012 (change in name of sponsor), 0017 dated 27 March 2013 (Updated Module 3), 0018 dated 4 March 2013 (information pertaining to last module for rolling BLA), 0022 dated 13 May 2013 (change of sponsor address) and 0031 dated September 25, 2013 (response to information request dated November 29, 2012 and August 30, 2013)]. For a review of the microbial controls in drug product manufacture and sterility assurance of drug product, please see the review by Dr. Steven Fong.

II. Recommendation and Conclusion on Approvability

Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective. The metreleptin drug substance is manufactured by Sandoz GmbH in Kundl, Austria. The site was inspected from August 16 - 24, 2012. A 3-item FDA form 483 was issued at the end of inspection. The inspection was classified as Voluntary Action Indicated (VAI). For the compliance status of the drug substance facility, please see final TB-EER.

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(b) (4)

CONCLUSION:

I. Sections 3.2.S of the BLA pertaining to microbial control of the drug substance manufacturing process were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.

II. CMC product specific information and data should be reviewed by the OBP reviewer.

III. The Sandoz GmbH facility located at Biochemiestrasse 10 Kundl,Tyrol A-6250, Austria was inspected by a team of investigators (Kalavati Suvarna, Ph.D., Susan Kirshner, Ph.D., and Cecilia Tami, Ph.D.) from August 16 - 24, 2012. A 3-item FDA form 483 was issued at the end of inspection. The inspection was classified as VAI. Please see final TB-EER for the compliance status of the manufacturing and testing sites.

SIGNATURES/DISTRIBUTION LIST

Primary BMAB Reviewer: Kalavati Suvarna, Ph.D. Date:
Concurring BMAB Team Leader: Patricia. F. Hughes, Ph.D. Date:

cc:
HFD-510/ Madara, Patricia
(b) (6) Hughes, Patricia
HFD-510/Nguyen, Christine
HFD-590/Roberts, Mary

Attachments:

Information request dated June 27, 2012.

(b) (4)


(b) (4)

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/s/

KALAVATI C SUVARNA
10/18/2013

PATRICIA F HUGHES TROOST
10/18/2013