CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125390Orig1s000

CHEMISTRY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1790

MEMORANDUM

From: Maria Cecilia Tami, PhD.
Through: Ennan Guan, MD, PhD
To: Susan Kirshner, PhD
Review Chief

Sponsor: Bristol-Myers Squibb
Product: Recombinant analog of human leptin, **MYALEPT (metreleptin for injection)**
Route: Subcutaneous injection
Indication: Treatment of metabolic disorders associated with lipodystrophy

Subject: **125390: Addendum to the Drug product review of the CMC section of the application.**

Recommendation:

Water for injection containing 0.9% benzyl alcohol (BWFI) is an acceptable diluent for MYALEPT and can be included in the label.

Background

At the time the reviews for this application were due in DARRTS, a final determination on the suitability of BWFI as a diluent for MYALEPT had not been made. The available information was insufficient to adequately demonstrate that the Sponsor understood the impact of Benzyl alcohol on product quality and on the performance of their release and stability testing methods. This addendum provides the rationale to support the acceptability of BWFI to be used as a diluent for MYALEPT for a multi use vial.

Myalept is supplied as a sterile, white, solid lyophilized cake containing 11.3 mg of metreleptin per vial. The content of the vial is reconstituted with 2.2 mL of water for injection (WFI) for a single dose or WFI containing 0.9% benzyl alcohol (BWFI) to allow for multiple doses over a period of up to 3 days.

Data from Myalept reconstituted in BWFI show a consistent increase in total oligomers measured by SEC-HPLC of approximately (b) (4) relative to MYALEPT reconstituted in WFI (please refer to table 21-2 of section 3.2.P.8.3 in

the CMC review memo for comparative testing for total oligomer content after reconstitution with WFI and BWFI). Moreover, results from the in use stability studies showed a further increase of (b) (4) in total oligomer content upon storage at (b) (4). However, these data were derived from a single lot (Lot 941352F, Table 29 of section 3.2.P.8.3 in the CMC review memo). Therefore, the Sponsor is required to confirm the in-use stability of MYALEPT reconstituted in BWFI with data derive from additional lots (please refer to PMR3 in the approval letter). The rational for the requirement is provided below (section rational for recommendation).

MYALEPT drug product release and stability testing were performed using lyophilized cake reconstituted in WFI, rather than BWFI, as most analytical procedures were validated using WFI. The limited data derived from testing MYALEPT reconstituted in BWFI were inconsistent with the results obtained with WFI for the oligomer content and osmolality tests. For example, non-dissociable oligomer content was (b) (4) when product was reconstituted with BWFI than when reconstituted with WFI for lot 592053F (compare release data and Table 30, unexposed control). Osmolality results for MYALEP lots reconstituted in BWFI were OOS results but were within the specification when the lots were reconstituted in WFI. Comparative testing for osmolality upon reconstitution with BWFI and WFI of batches used in pivotal or supporting clinical studies showed that reconstitution with BWFI increases osmolality by an average of 86 mOsm/Kg over reconstitution with WFI.

At the late cycle meeting held in November 21st, 2013, FDA conveyed these concerns to the sponsor and requested that the Sponsor provide a comprehensive written explanation on their knowledge on the impact of BWFI on product quality and method performance together with their proposed overall strategy to control the quality of MYALEPT reconstituted in BWFI.

A follow up teleconference was held in December 16, 2013. The Sponsor's presentation discussed during the teleconference is included in attachment 1 to this addendum.

During the teleconference the Sponsor explained that total oligomers is a quality attribute of metreleptin that is affected by BFWI reconstitution and proposed to include in the release and stability specifications an additional acceptance criterion for total oligomer content upon reconstitution with BWFI. (b) (4)

Based on available data obtained from retrospective testing of all drug product lots manufactured at (b) (4) upon storage at (b) (4) the Sponsor proposed an acceptance criteria of NMT (b) (4) for total oligomer content in drug product reconstituted in BWFI, (b) (4) than the proposed acceptance criteria for total oligomer content using WFI (NMT (b) (4). The proposed acceptance limit of NMT

(b) (4) for oligomer content for release and stability may be revised based on data derived from a statistically meaningful number of production scale DP lots as part of a post-marketing committeemen (please, refer to PMC 4 of the approval letter).

With regards to osmolality testing, the Sponsor indicated that benzyl alcohol in the BWFI added to the total osmolality of the reconstituted product as expected. Because the osmolality test is meant to determine whether the formulation was correct the sponsor proposed to continue testing osmolality after reconstitution in WFI to more efficiently monitor and control drug product formulation.

Rational for the recommendation

Metreleptin is a replacement therapy for treating lipodystrophy. Generalized lipdystrophy is a very rare disease (~1:10,000,000) for which there is no treatment. Lipodystrophy patients lack adipose tissue and therefore have disregulated metabolism and very high serum triglycerides and cholesterol. This can lead to cardiovascular problems and premature death. Adipose tissue is the main source of leptin in humans, although other cells such as cells of the immune system also produce leptin. The development of neutralizing antibodies was linked to loss of efficacy and/or loss of endogenous leptin activity in five patients receiving metreleptin treatment. Three of those patients are in the obese population in which metreleptin will be counterindicated.

Although the risk of a (b) (4) in total oligomer content seems low, it is theoretically possible that this difference contributes to the development of anti-drug antibodies. However, other factors are more likely to impact anti-drug antibody formation such as the intrinsic immunomodulatory properties of metreleptin and its effect on homeostasis and function on T regulatory cells. In addition, metreleptin is formulated at a pH of 4.25 due to its low solubility at higher pH conditions. Therefore, metreleptin could potentially precipitate in the higher (neutral) pH of the subcutaneous environment, which may contribute to the product's immunogenicity..

Metreletpin can be reconstituted in WFI for a single dose or in WFI containing 0.9% benzyl alcohol (BWFI) to allow for multiple doses over a period of up to 3 days. Reconstitution with BWFI results in a consistent increase of approximately (b) (4) in oligomer content relative to MYALEPT reconstituted in WFI. Results from the in-use study with a single lot show a further increase of (b) (4) when stored at (b) (4) for 3 days. The Sponsor set release and stability specifications for total oligomer content upon reconstitution with BWFI to monitor and control for this attribute change. Further, because results from only one lot were used to establish the in use stability of MYALEPT reconstituted in BWFI, they are required to confirm the in-use stability of MYALEPT reconstituted in BFWI with data derived from additional drug product lots post approval. This approach will ensure that the levels of oligomer content remain consistent with those of the clinical lots.

<u>Reviewer comment:</u> BFWI was the sole diluent for metreleptin since 2007 to allow for multi-dose use of metreleptin in clinical trials. Therefore, the safety and efficacy profiles of MYALEP reconstituted in BWFI are well established. As discussed above, it is unlikely that the immunogenicity of the drug is due to a slight increase in non dissociable aggregates compared to MYALEPT reconstituted in WFI. The sponsor provided an adequate rationale for continuing to use WFI as the diluent for the osmolality test. Therefore, the use of BWFI as diluent for MYALEPT for multi dose use is acceptable.

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/s/

Maria Cecilia TAMI
02/20/2014

ENNAN GUAN
02/20/2014

SUSAN L KIRSHNER
02/20/2014

Department of Health and Human Services Office of Biotechnology Products
Food and Drug Administration Division of Therapeutic Proteins
Center for Drug Evaluation and Research Rockville, MD 20852

Date: 2/14/2014

STN: BLA 125390 (corresponding IND 101,24)

From: Laura I. Salazar-Fontana, Ph.D.

Through: Susan L. Kirshner, Ph.D.
Review Branch Chief
Division of Therapeutic Proteins
Office of Biotech Products
CDER/FDA

Subject: Immunogenicity review for Metreleptin for Injection, 11.3 mg/ 2.2 mL (5mg/mL), subcutaneous (s.c.) injection once daily.

Indication: Treatment of diabetes and hypertriglyceridemia associated with congenital or acquired lipodystrophy.

Sponsor: Amylin, subsidiary of Brystol-Myers Squibb Company

RECOMMENDATION: Approval with Post-Marketing Requirements.

JUSTIFICATION:

Metreleptin is highly immunogenic as can be concluded from the development of anti-metreleptin antibodies in almost all patients receiving metreleptin treatment. Moreover, clinical symptoms of inhibition of metreleptin and leptin activity were observed in patients, with loss of efficacy and increased incidence of infections reported.

We noted a number of problems with the analytical methods.

- *The* (b) (4) *assay used to screen for anti-metreleptin antibodies for some of the samples lacked sensitivity. This assay was replaced by a more sensitive ECL based assay, but not all samples were retested using that more sensitive assay.*
- *The screening and neutralizing assay cut-points established using serum samples from healthy donors were not confirmed using serum from lipodystrophy patients. Therefore it is not clear that appropriate cut-points were used to decide whether patient samples were antibody or neutralizing antibody positive.*

- *Neutralizing antibody activity is measured using a cell based assay. Matrix interference studies indicate that the cells may respond to levels of leptin and metreleptin that can be present in test samples. This can decrease assay sensitivity, leading to under reporting of neutralizing antibodies in patients.*

- *The lack of systematic sample collection in Studies NIH991265 and NIH20010769 prevents accurate evaluation of antibody response, magnitude, and persistence.*

Given the limitations described above limitations, we are concerned that the number of anti-metreleptin positive samples is under reported.

Despite these limitations, in clinical trials NIH991265, NIH20010769, and FHA 101, 86% of patients tested positive for anti-metreleptin antibodes in the screening assay, 84% (36/43) of generalized lipodystrophy patients, and 89% (31/35) of partial lipodystrophy patients. Six per cent of patients with generalized lipodystrophy tested positive in the neutralizing assay. One generalized lipodystrophy patient who tested positive for neutralizing antibodies lost metreleptin efficacy, as evidenced by increased serum triglycerides, and had five episodes of sepsis during peak NAb responses observed at month 24 of treatment. As leptin is involved in immune regulation, this susceptibility to infection may have resulted from loss of endogenous leptin activity due to the presence of neutralizing antibodies. In the past month another lipodystrophy patient showed signs of loss of efficacy and tested positive for neutralizing antibodies. Additional information on this patient is pending.

Given the pivotal role that the native protein plays in the immune system, we believe that adequate antibody testing is of paramount relevance to understanding the safety profile of metreleptin. However, the deficiencies in assay validation and sample collection can be addressed in the context of the post-marketing requirements and commitments listed below because:

- *generalized lipodystrophy is a rare life threatening disease,*
- *the majority of patients with neutralizing antibodies that received metreleptin treatment did not show clinical sequelae,*
- *patients who showed signs of loss of efficacy or endogenous leptin activity tested positive for NAb,*
- *and the distribution of this drug will be limited to generalized lipodsytrophy patients*

PMR#1: "To develop, validate, and implement a ligand binding assay to supplement the neutralizing bioassay that tests for the presence of neutralizing antibodies in serum samples from patients with generalized lipodystrophy."

Rationale: FDA guidance recommends that NAb assays for proteins that act as agonists be bioassays, as NAb activity in a bioassay better reflects biological activity in vivo. However, in cases where matrix interference from the test articles can confound the assay results then non-cell based assays to measure the ability of NAb to interfere with receptor ligand interactions are used to verify negative results in the bioassay.

PMR#2: "To conduct a study to assess for the immunogenicity Myalept (metreleptin) in a (b) (4) *relevant number of patients receiving metreleptin. The study should include testing of anti-metreleptin and anti-native human leptin binding antibodies at times when antibody responses peak using a validated assay. The presence of neutralizing antibodies should be* (b) (4) *using a validated cell-based assay and a validated ligand-binding assay in samples that are confirmed positive for binding antibodies to leptin. All patients with suspected loss of metreleptin efficacy (e.g., worsening glycemic control, increases in triglycerides) or loss of endogenous leptin activity (e.g., severe infections) should be tested for neutralizing activity and followed up until antibody levels revert to baseline. Antibody titers, neutralizing activity, and associated clinical events should be characterized over time."*

Rationale: This study will provide missing information on the natural history of anti-metreleptin antibodies in patients.

PMR#3: "To test all banked clinical samples from pivotal clinical studies NIH 991265/20010769 and study FHA101 for the presence of neutralizing antibodies against leptin using the ligand binding assay developed and validated under PMR (b) (4) *and to correlate neutralizing antibodies with clinical events."*

Rationale: The lack of sensitivity of the bioassay used to determine the presence of NAbs in samples from patients enrolled under the two supporting pivotal studies NIH 991265/20010769 and FHA101 raise a concern over underreported number of NAb positive patients. Given the concern over loss of efficacy to metreleptin treatment and the potential loss of endogenous leptin function, testing of banked clinical samples with a ligand binding assay with reduced matrix interference and increased sensitivity would allow identification of samples with low levels of neutralizing antibodies that were not detected with using the existing cell-based assay.

REVIEW of Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies.

IMMUNOGENICITY ASSAYS

The application describes the use of three different assays to determine the presence of anti-metreleptin antibodies (ADAs): two ligand binding platforms for screening of total ADAs ((b) (4) and electrochemiluminescence or ECL) and a cell-based assay to evaluate the presence of neutralizing antibodies (NAbs). At least, four different sensitivities are described for the screening and neutralizing assays.

The safety database for metreleptin includes data from two different patient populations: lipodystrophy (proposed indication) and obesity patients. The obesity database includes data on patients treated with metreleptin alone or in combination with pramlintide.

The clinical addendum submitted in 2012 contained two tables listing document identification numbers and types to help identify the relevant validation reports. SOPs were also included and are the documents classified as "method" under the document type column in Tables 3 and 4.

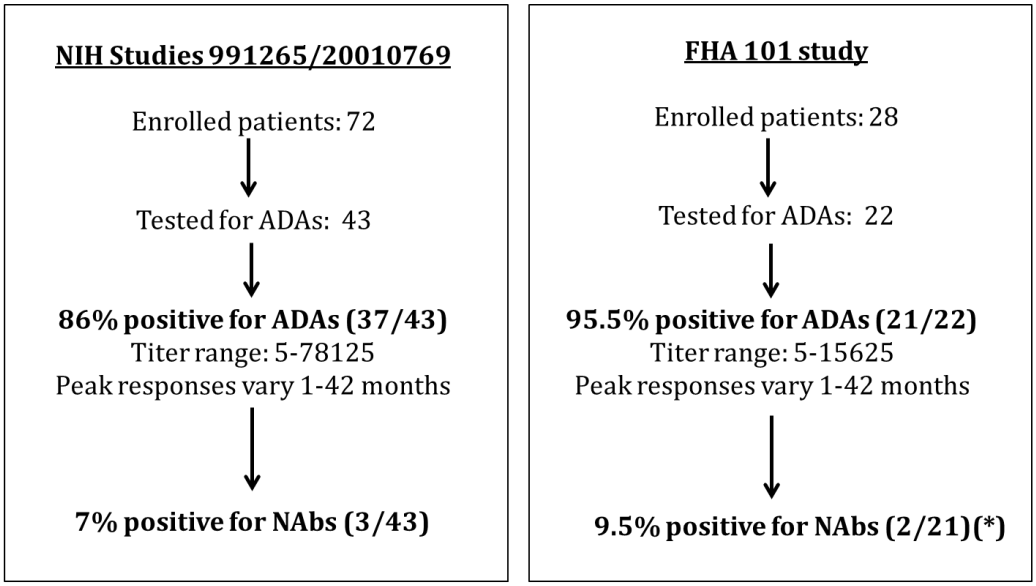
was determined to be approximately 0.25 µg/mL. Because the current sensitivity of the method is in agreement with FDA guidance, development of a ligand-binding method was not pursued.

General comment: The validated cell based assay shows poor sensitivity in the presence of leptin levels that may be present in serum samples, low drug tolerance, and high degree of matrix interference due to the inability to discriminate between native and recombinant leptin. Therefore, the limitation of the assay cannot be fully explained by recalculation of the assay sensitivity using a different PC as approached by the sponsor. A recommendation was made to consider the development of a ligand-based assay to support analysis of NAb given the limitation of the biological assay. I consider that the response provided still does not account for the limitations of the current assay and therefore, I recommend that a ligand-based approach is further explored.

IMMUNOGENICITY DATA

The immunogenicity database for this BLA includes data obtained from samples collected from two different populations: lipodystrophy (proposed indication) and obesity (halted studies). Since this BLA is seeking approval for the treatment of metabolic disorders associated with paucity of fat tissue in lipodystrophy patients, only that set of data will be discussed in this review.

The scheme below summarizes the data on total anti-metreleptin antibodies of binding and neutralizing activity that was discussed during the Advisory Committee meeting that took place on December 11th, 2013. The reported antibody incidence includes testing of samples from patients diagnosed with generalized and partial lipodystrophy.



(*) In the four month safety update, a third patient in FHA101 tested positive for NAbs

The NIH study enrolled the largest number of patients, with a total of 72, with data on ADAs collected from 43 out of those 72 patients. ADAs were detected in 86% of the patients tested out of the NIH studies, with titers ranging between five and seventy eight thousand and peak responses varying between month 1 and 42.

Reviewer comment: A major deficiency in the patient data is that samples were not systematically collected. For example most patients did not have samples taken around day 14 and day 28 after the first

dose and every 3 months thereafter. Rather, samples seem to have been collected at random time points that varied between patients, e.g. T0 and month 8; T0 and month 12 or 18. This precludes developing an understanding of the natural history of ADA and NAb development in metreleptin treated patients. This is a significant problem because anti-metreleptin antibodies caused deficiency syndromes in several obese patients and in two lipodystrophy patients. In the three obese patients who developed deficiency syndromes anti-metreleptin antibodies were detected four years after drug treatment stopped, suggesting that tolerance to endogenous leptin had been broken. The two lipodystrophy patients with repeated episodes of sepsis are still being followed. Because of the serious clinical ramifications of anti-metreletin NAb, a PMR to study ADA development in generalized lipodystrophy patients will be requested.

Three patients were identified as positive for NAbs. We considered as Nab positive all those patients who tested positive above the established neutralizing assay cut point when analyzed at a minimal required dilution of 1:80.

From the ongoing FHA101 study, we evaluated the data obtained on ADAs from 22 out of a total of twenty eight patients enrolled. The observed incidence in ADAs was 95.5%. Antibody titers ranged between five and fifteen thousand, with similar peak responses as the ones described for patients enrolled in the NIH study.

Two patients were identified as positive for neutralizing activity with a third patient reported as positive in the four month safety update provided in July 2013.

According to the sponsor, all samples from the NIH and FHA101 studies were tested for neutralizing activity regardless of their positivity for binding antibody. Neutralizing activity was determined by calculating the inhibition of activity ratio between the pre-dose and the post-dose value obtained for each serum sample.

Test samples from patients in study FHA101 studies were assessed using the validated (b) (4) method whereas samples from patients in the NIH studies were assessed at Amylin using a qualified ECL method.

Each serum sample tested was classified by its ability to inhibit proliferation of cells of the 32D OBECA cell line when tested at 5 different 1:10 serum dilutions starting from the established minimal required dilution (MRD) of 1:80.

(b) (4)

The categorization described in Table 5 was used to report the results on neutralizing activity obtained at (b) (4) and Amylin testing sites.

Reviewer's comment: We do not agree with (b) (4) *We have considered as NAb positive samples all those where an inhibition above the established cut point (PIMet) of* (b) (4) *was observed in accordance with current antibody incidence reporting recommendations as the number of samples that should be reported under the final label.*

IMMUNOGENICITY RISK ASSESSMENT

Human leptin, is produced by mature adipocytes located mostly in the white adipose tissue. It functions by regulating the organism's energy balance by controlling food intake and/or regulating energy expenditure to maintain constancy of the adipose mass (*Margetic, S. et al., 2002*). It shares an 85% amino acid sequence homology with its murine and rat counterparts. Leptin is the product of the *ob* gene located on Chromosome 7 in humans and chromosome 6 in mice (*Zhang, Y. et al., 1994*). Mutations in this gene and/or its regulatory regions cause severe and morbid obesity with hypogonadism. This gene has also been linked to type 2 diabetes mellitus development (*Matarese, G. et al., 2012*). Native leptin is translated as a 167 amino acid precursor with an amino terminal secretory signal sequence of 21 amino acid that is cleaved to render a as a 146 amino acid protein that circulates in the blood.

In addition to its role in metabolism, leptin plays a pivotal role in the immune system homeostasis. Leptin can control: the proliferation of naïve and memory T cells (*Lord et al., 1998*); the secretion of pro-inflammatory cytokines by T cells (Th1 differentiation) *(Lord et al., 1998)*; IgG2a secretion by B cells (*Martin-Romero et al., 2001)*; and the proliferation and expansion of CD4+ CD25+ FoxP3 T lymphocytes (Tregs) with sustained suppressive capacity both *in vitro* and *in vivo* (*De Rosa et al., 2007*). Furthermore, the analysis of the immune system of animals deficient in leptin or its receptor show increased circulating numbers of Tregs that can be restored to normal levels by leptin administration (*Matarese et al., 2001; Sanna et al., 2003; Siegmund et al., 2004; Faggioni et al., 2000; Lee et al., 2005*) but most importantly, the deficiency in either leptin or its receptor render the animals more susceptible to infections (*Matarese et al., 2002*) and resistant to autoimmunity (*Matarese et al., 2012*), supporting the role of this protein in pro-inflammatory processes. Similar observations have been made out of a genealogic study conducted in a family carrying a missense mutation in the leptin gene. Those individuals that were born with the obese phenotype died earlier in life due to increased incidence of infections (*Ozata et al., 1998)*, supporting the data observed knockout animal models.

Product-related factors and patient-related factors can also contribute to the immunogenic potential of therapeutic proteins. Metreleptin is a recombinant form of the human leptin, expressed in *Escherichia coli (E. coli)*. It differs from the human protein by the addition of a methionine residue at its amino terminus. No glycosylation is present in either the recombinant or the native protein. The impurity analysis of metreleptin shows that [redacted (b) (4)] The observed degradation products are the ones typically observed for other recombinant proteins and the degree of oligomerization observed in the lots used in the clinical trials does not go above [redacted (b) (4)] of the total product. In conclusion, these factors together with the daily subcutaneous administration of metreleptin may contribute to the high immunogenicity observed but are not considered as high risks factor for unwanted clinical sequelea.

However, the non- redundant biological role of leptin in metabolic control, and in the immune system, place this therapeutic protein at high risk for development of serious adverse events mediated by the presence of anti-metreleptin antibodies that could cross-react with the endogenous protein.

The consequences of interfering with the leptin/leptin receptor pathway and its impact in the function of the immune system of patients receiving the treatment deserve further evaluation. In these populations, the presence of antibodies that could cross-react and neutralize the function of the native protein could result in increased susceptibility to infections due to dysregulation of T cell homeostasis. This conclusion is supported by the observation of increased incidence of sepsis events that required clinical intervention in one lipodystrophy patient enrolled under study FHA101 when maximal anti-drug antibody titers were also observed.

Additionally, loss of efficacy due to the presence of high titers of NAbs has been reported among obese patients and has resulted in discontinuation of metreleptin treatment in this population.

Reviewer's comment: In conclusion, despite the limitations in the methods used to assess the presence of anti-metreleptin antibodies described in detail under the review of the methods validation reports; we can conclude that almost all patients receiving metreleptin treatment develop detectable levels of anti-leptin antibodies. Moreover, neutralizing activity was observed in patients where loss of efficacy and increased incidence of infections have been identified and reported.

We are concerned about under reported number of samples that have either low antibody concentrations or are misclassified as negatives early during treatment. Additionally, the lack of systematic data collection prevents evaluation of antibody response magnitude and persistence.

Given the pivotal role that the native protein plays in the immune system, we believe that adequate antibody testing is of paramount relevance to understand the safety profile of this therapeutic protein.

The sponsor will be asked to address these concerns in the context of post-marketing requirements.

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/s/

LAURA I SALAZAR FONTANA
02/14/2014

SUSAN L KIRSHNER
02/14/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

APPLICATION INFORMATION

PDUFA Action Date: 02/24/2014

Applicant Name: Amylin Pharmaceuticals, Inc.
U.S. License #: 1854
STN(s): 125390
Product(s): Metreleptin
Summary: BLA proposing manufacture of metreleptin drug product at the [redacted] (b) (4)

Reviewer Comment: This is the final TB-EER request for this submission. The initial request was submitted 05/22/2013 and a response was received 05/31/2013.

FACILITY INFORMATION

Firm Name: [redacted] (b) (4)
Address:

FEI:
Short summary of manufacturing activities performed:

- [redacted] (b) (4) drug product manufacture
- Packaging
- Labeling
- Sterility and endotoxin release testing

This site was inspected by [redacted] (b) (4) from [redacted] (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering sterile drug product manufacturing operations. The [redacted] (b) (4) profiles were updated and are acceptable

Firm Name: Sandoz GmbH (Sandoz)
Address: Biochemiestrasse 10, Kundl, Tyrol A-6250, Austria
FEI: 3002806523
Short summary of manufacturing activities performed:

- Drug substance manufacturing.

This site was inspected by IOG from October 3 – 12, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. The CBI profile was updated and is acceptable.

Firm Name: (b) (4)
Address:

FEI:
Short summary of manufacturing activities performed:

- Sterility and endotoxin stability testing

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

Firm Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive
San Diego, CA 92121
FEI: 1000519848
Short summary of manufacturing activities performed:

- Release testing (except sterility and endotoxin testing) of drug product and drug substance.
- Stability sample storage
- Stability testing (except sterility and endotoxin stability testing)
- Bioassay reagent cell bank storage.

This site was inspected by LOS-DO from March 25 – 27, 2013 and classified NAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

Firm Name: (b) (4)
Address:

FEI:
Short summary of manufacturing activities performed: Bioassay reagent cell bank manufacturing and storage

This site was inspected by (b) (4) from (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing and cell banking operations. The CTL profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this BLA.

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/s/

RANJANI PRABHAKARA
02/11/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

APPLICATION INFORMATION

PDUFA Action Date: 02/24/2014

Applicant Name: Amylin Pharmaceuticals, Inc.
U.S. License #: 1854
STN(s): 125390
Product(s): Metreleptin
Summary: BLA proposing manufacture of metreleptin drug product at the (b) (4)

Reviewer Comment: This is the final TB-EER request for this submission. The initial request was submitted 05/22/2013 and a response was received 05/31/2013.

FACILITY INFORMATION

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed:

- (b) (4) drug product manufacture
- Packaging
- Labeling
- Sterility and endotoxin release testing

Firm Name: Sandoz GmbH (Sandoz)
Address: Biochemiestrasse 10, Kundl, Tyrol A-6250, Austria
FEI: 3002806523

Short summary of manufacturing activities performed: Drug substance manufacturing.

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed: Sterility and endotoxin stability testing.

Firm Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive
San Diego, CA 92121
FEI: 1000519848

Short summary of manufacturing activities performed:

- Release testing (except sterility and endotoxin testing) of drug product and drug substance.
- Stability sample storage
- Stability testing (except sterility and endotoxin stability testing)
- Bioassay reagent cell bank storage.

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed: Bioassay reagent cell bank manufacturing and storage

OVERALL RECOMMENDATION

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/s/

PATRICIA J MADARA
02/04/2014

BLA STN 125390

Product USAN name: Metreleptin

Manufacturer: Bristol-Myers Squibb

Reviewer: Laura I Salazar-Fontana
Reviewer: Maria Cecilia Tami
Reviewer: Montserrat Puig
Secondary reviewer: Ennan Guan
Tertiary Reviewer: Susan Kirshner
Division of Therapeutic Proteins

OBP CMC Review Data Sheet

1. **BLA#:** STN 125390

2. **REVIEW DATE:** December 19th, 2013

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Julie Golden/ Jim Smith/ Eric Colman
Pharm/Tox: Federica Basso/Todd Bourcier
Product Quality Team: Laura I. Salazar-Fontana, Maria Cecilia Tami, Montserrat Puig/ Ennan Guan/ Susan L. Kirshner
BMT or Facilities: Kalavati Suvarna, Steven Fong/ Patricia Hughes
Clinical Pharmacology: Jaya Vaidyanathan/Immo Zadezensky
Statistics: Bradley McEvoy/ Mark Rothmann
OBP Labeling: Kim Raines
RPM: Patricia Madara

4. **MAJOR GRMP DEADLINES**

Filing Meeting: April 30th, 2013
Mid-Cycle Meeting: September 18th, 2013
Late-Cycle meeting: November 20th, 2013
Wrap-Up Meeting: January 10th, 2014
Primary Review Due: November 27th, 2013
Secondary Review Due: December 2nd, 2014
CDTL Memo Due: February 1st, 2014
PDUFA Action Date: February 27th, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	December 12th,2013
Teleconference 1	Mid-cycle: September 18th, 2013
Information Request #1	August 19th, 2013
Information Request #2	October 8th, 2013
Teleconference 2	December 16th, 2013

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 125390/0017 (Amendment 018)	March 27th, 2013	Yes
STN 125390 /4 (response to IR #1)	Spetember 16th, 2013	Yes

STN 125390 /0042 (response to IR #2)	11/7/2013	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: AC164594
   b. Trade Name: Myalept
   c. Non-Proprietary/USAN: metreleptin
   d. CAS name: r-metHuLeptin
   e. Common name: Leptin
   f. INN Name: Leptin or OB protein
   g. OBP systematic name: RPROT P41159 (LEP_HUMAN) Metreleptin [AC164594]

8. **PHARMACOLOGICAL CATEGORY:** Hormone (adipokine) that exerts its function by binding to the ObR belonging to the Class I cytokine family of receptors that signals through the JAK/STAT pathway.
9. **DOSAGE FORM:** Injection (10 mg/vial)
10. **STRENGTH/POTENCY:**
   (i) The concentration/strength of the Drug Product: 5 mg/ml (upon reconstitution): 2.5 mg for males (0.5 mL) and 5.0 mg for females (1.0 mL).
   (ii)

Table 1: Metreleptin Recommended Daily Dose by Weight and Gender

Baseline Weight	Daily Dose (Injection Volume)
≤40 kg (males and females)	0.06 mg/kg (0.012 mL/kg)
>40 kg	
Males	2.5 mg (0.5 mL)
Females	5.0 mg (1.0 mL)

   (ii) Type of potency assay (s): bioassay: proliferation of leptin receptor transfected cell line.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous injection (s.c.)
12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted] (b) (4)			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No review required as all the relevant information related to compatibility with the product

(b) (4)		
		was in the BLA
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

13. INSPECTIONAL ACTIVITIES

A pre-license inspection of the metreleptin drug substance manufacturing facility was conducted following a request by the Biotech Manufacturing Assessment Branch, Office of Compliance, CDER under FACTS assignment #1429743 (Inspection No. TFRB-12-11; OPID 6271689). The inspection covered the manufacturing operations for BLA STN 125390 for metreleptin drug substance at Sandoz GmbH, Biochemiestrasse 10, Kundl, Tyrol A-6250, Austria.

The inspection was conducted in accordance with applicable sections of CP 7356.002M, Inspection of Licensed Therapeutic Drug Products and ICH Q7. This inspection was limited to the manufacture of metreleptin. This inspection covered the following main systems: Quality, Facilities and Equipment, Production, Materials, and Laboratory.

The FDA personnel involved in the inspection included: Kalavati Suvarna, Ph.D., microbiologist (BMAB, OC, CDER); Susan Kirshner, Ph.D., Supervisory Biologist (DTP, OBP, CDER) Maria Cecilia Tami, Ph.D., Senior Staff Fellow (DTP, OBP, CDER)

The current inspection revealed CGMP deficiencies. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued to Mr. Ernst Meijnders, Head Business Unit Anti-Infectives & API, Chief Executive Officer. The observations were as follows:

Observation listed on form FDA 483:

(b) (4)

(b) (4)

The firm agreed with the observation and committed to sending a written response to CDER/OC/OMPQ/ICB.

As per BMAB recommendation, the inspection of the DP facility was waived based on a recent inspection of (b) (4) the current manufacturer of metreleptin DP

14. CONSULTS REQUESTED BY OBP

Statistical consult (OTS/OB/DBVI) requested on August 21, 2013. Assigned reviewer: Dr. Meiyu Shen. Completed October 8th, 2013. To evaluate the adequacy of the statistical approach used to evaluate the kinetics of degradation of metreleptin DP.

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS

No manufacturing or regulatory precedent setting decisions were made during this review

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Susan Kirshner Ph.D Regulatory Review Chief, Division of Therapeutic Proteins Ennan Guan, M.D., Ph.D. Team Leader, Division of Therapeutic Proteins	December 19th, 2013
Laura I. Salazar-Fontana, Ph.D. Maria Cecilia Tami, Ph.D. Montserrat Puig, Ph.D. Primary Reviewers, Division of Therapeutic Proteins	December 19th , 2013

B. CC Block

Recipient	Date
Patricia Madara Clinical Division BLA RPM	December 19th , 2013
Division of Therapeutic Proteins File/BLA STN 125390	

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/s/

LAURA I SALAZAR FONTANA
12/19/2013

MONTSERRAT PUIG
12/19/2013

ENNAN GUAN
12/19/2013

JUHONG LIU on behalf of SUSAN L KIRSHNER
12/20/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.1

APPLICATION INFORMATION

PDUFA Action Date: 11/25/2013

Applicant Name: Amylin Pharmaceuticals, Inc.
U.S. License #: 1854
STN(s): 125390
Product(s): Metreleptin
Summary: BLA proposing manufacture of metreleptin drug product at the (b) (4)

FACILITY INFORMATION

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed:

- (b) (4) drug product manufacture
- Packaging
- Labeling
- Sterility and endotoxin release testing

Firm Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive
San Diego, CA 92121
FEI: 1000519848

Short summary of manufacturing activities performed:

- Release testing (except sterility and endotoxin testing)
- Stability sample storage
- Stability testing (except sterility and endotoxin stability testing)
- Bioassay reagent cell bank storage.

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed:

- Sterility and endotoxin stability testing

(Firm list continued on page 2)

Firm Name: (b) (4)
Address:

FEI:

Short summary of manufacturing activities performed:

- Bioassay reagent cell bank manufacturing and storage

OVERALL RECOMMENDATION

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/s/

STEVEN FONG
05/22/2013

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & OMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125390	Amylin Pharmaceuticals, Inc.,	April 3, 2012
Established/Proper Name: Metreleptin	**BLA/NDA Type:** Original	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
❑ including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y	
❑ Patient Insert	Y	
❑ package and container	Y	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & OMPQ)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	OBP Lead
❑ Novel Excipients	N	Drug product contains no novel excipients.
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y N	OBP Lead
❑ Comparability Protocols	Y N	OBP Lead

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	Y	Shipping validation studies and data were not included
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	Y N	OBP Lead
❑ control of critical steps and intermediates o justification of specifications o stability	Y	In-process bioburden limits will be a review issue. Additional information will be requested from the applicant.

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & OMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	Shipping validation and data missing
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	OBP Lead
❑ characterization of drug substance		
❑ control of drug substance		
o specifications		
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation		
o batch analyses		
❑ reference standards	Y N	OBP Lead
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	N	
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation		
o Component, container, closure depyrogenation	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation		
o Validation of aseptic processing (media simulations)	Y	
o Environmental Monitoring Program	Y	
o Lyophilizer validation	Y	
o Other needed validation data (hold times)	Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP Lead
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y N	OBP Lead
❑ container closure system [3.2.P.7]	Y	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
o administration device(s)		
❑ stability	Y	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Diluent (vials or filled syringes) [3.2P′]		Lyophilized product is to be reconstituted with WFI or bacteriostatic WFI. The diluent is not provided with product.
❑ description and composition of diluent	N	
❑ pharmaceutical development	N	N/A. Diluent not provided.
o preservative effectiveness		
o container-closure integrity	N	N/A. Diluent not provided.
❑ manufacturers (names, locations, and responsibilities of all sites involved)	N	N/A. Diluent not provided.
❑ batch formula	N	N/A. Diluent not provided.
❑ description of manufacturing process for production through	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	N	N/A. Diluent not provided.
❑ process validation including aseptic processing & sterility assurance:	N	N/A. Diluent not provided.
o Filter validation		
o Component, container, closure depyrogenation and sterilization validation	N	N/A. Diluent not provided.
o Validation of aseptic processing (media simulations)		
o Environmental Monitoring Program	N N	N/A. Diluent not provided. N/A. Diluent not provided.
o Lyophilizer sterilization validation		
o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	N	N/A. Diluent not provided.
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	N	
❑ reference standards	N	
❑ container closure system	N	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
❑ stability	N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		Product does not include other components.
❑ other devices	Y N	Not applicable
❑ other marketed chemicals (e.g. part	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y Y N	OBP Lead OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y Y N Y N	OBP Lead OBP Lead OBP Lead
Literature references and copies [3.3]	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP Lead
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP Lead
Data demonstrating comparability of	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	OBP Lead
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y Y Y Y	 OBP Lead
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	OBP Lead
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & OMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide the shipping validation study protocol and data to support shipping of drug substance from the Sandoz drug substance manufacturing site located at Kundl, Austria to the (b) (4) drug product manufacturing site located at (b) (4).
2. Please provide your microbial control strategy for the drug substance manufacturing steps. A justification for the in-process bioburden limits at the different manufacturing steps should be included.
3. Please clarify the steps of the manufacturing process that use (b) (4).

Kalavati Suvarna, Ph.D. Date
Drug Substance Microbiology Reviewer
OC/OMPQ/DGMPA/BMAB

Steven Fong, Ph.D. Date
Drug Product Microbiology Reviewer
OC/OMPQ/DGMPA/BMAB

Patricia Hughes, Ph.D. Date
Team Leader
OC/OMPQ/DGMPA/BMAB

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/s/

KALAVATI C SUVARNA
05/14/2012

STEVEN FONG
05/15/2012

PATRICIA F HUGHES TROOST
05/15/2012

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125390 **Applicant:** Amylin's Pharmaceuticals INC. **Stamp Date:** 3/27/2013

Established/Proper Name: Metreleptin **BLA/NDA Type:** Amendment to an original BLA application

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
❑ including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing arrangement	Y N	N/A

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Quality overall summary [2.3]	Y	N	
❑ Drug Substance	Y	N	
❑ Drug Product	Y	N	
❑ Facilities and Equipment	Y	N	
❑ Adventitious Agents Safety Evaluation	Y	N	
❑ Novel Excipients	Y	N	
❑ Executed Batch Records	Y	N	
❑ Method Validation Package	Y	N	
❑ Comparability Protocols	Y	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
❑ general info	Y	N	
o nomenclature	Y		
o structure (e.g. sequence, glycosylation sites)	Y		
o properties	Y		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
❑ description of manufacturing process and process control	Y	N	
o batch numbering and pooling scheme	Y		
o cell culture and harvest	Y		
o purification			
o filling, storage and shipping	Y		
❑ control of materials	Y	N	
o raw materials and reagents	Y		
o biological source and starting materials	Y		
o cell substrate: source, history, and generation	Y		
o cell banking system, characterization, and testing	Y		
❑ control of critical steps and intermediates	Y	N	
o justification of specifications	Y		
o stability	Y		
❑ process validation (prospective	Y		

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions)	Y N	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y	
❑ control of drug substance	Y	
o specifications	Y N	
o justification of specs.	Y N	
o analytical procedures	Y	
o analytical method validation	Y	
o batch analyses	Y N	
❑ reference standards	Y N	
❑ container closure system		
❑ stability	Y N	
❑ summary	Y N	
❑ post-approval protocol and commitment	Y N	
❑ pre-approval	Y N	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y N	
❑ pharmaceutical development	Y N	
o preservative effectiveness	Y N	
o container-closure integrity	Y N Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance:	Y N	
o Filter validation	Y	
o Component, container, closure depyrogenation and sterilization	Y	

CTD Module 3 Contents	Present?		If not, justification, action & status
validation			
○ Validation of aseptic processing (media simulations)	Y		
○ Environmental Monitoring Program	Y		
○ Lyophilizer validation	Y		
○ Other needed validation data (hold times)	Y		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N	
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	N	
❑ reference standards or materials	Y	N	
❑ container closure system [3.2.P.7]	Y	N	
○ specifications (vial, elastomer, drawings)	Y		
○ availability of DMF & LOAs	Y		
○ administration device(s)	Y		
❑ stability	Y	N	
❑ summary	Y		
❑ post-approval protocol and commitment	Y		
❑ pre-approval	Y		
○ protocol	Y		
○ results	Y		
○ method validation	Y		
Diluent (vials or filled syringes) [3.2P′]			N/A. Only vials with lyophilized DP
❑ description and composition of diluent	Y	N	
❑ pharmaceutical development	Y	N	
○ preservative effectiveness	Y	N	
○ container-closure integrity	Y		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
❑ batch formula	Y	N	
❑ description of manufacturing process for production through finishing, including formulation,	Y	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N Y N	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance: o Filter validation o Component, container, closure depyrogenation and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer sterilization validation o Other needed validation data (hold times)	Y N Y N Y N Y Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF & LOAs	Y N Y Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N Y Y Y Y	
Other components to be marketed (full description and supporting data, as listed above):		N/A
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

CTD Module 3 Contents	Present?	If not, justification, action & status
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y N Y N Y Y Y Y Y Y Y N	Since metreleptin is produced in the bacteria *E. coli*, no major adventitious agent studies are required.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y N Y N Y N	Method validation reports are included under DP Validation of Analytical Procedures.
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y N	
Includes data demonstrating consistency of manufacture	Y N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
Data demonstrating comparability of product to be marketed to that used in	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y N	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	(b) (4) therefore the stability of the new DP will be approved based on the approval of the comparability data and the implementation of bioburden controls.
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y N Y N Y N Y N	BMAB
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	BMAB
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	BMAB
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	BMAB

PRODUCT QUALITY (Biotechnology)

FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? **Yes** **No**

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

All the information required for the review of product quality is provided in the submission. The only documentation missing was the document on "Environmental assessment or request for categorical exclusion (21 CFR Part 25)".

The sponsor clarified that the missing information was included in the second portion of the rolling BLA submission on April 2, 2012, Serial 0003, Section 1.12.14. Amylin/BMS were asked to update the current BLA submission by adding this information under Module 1, Administrative Information section of the eCTD document.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at the time of filing.

LAURA I. SALAZAR-FONTANA, Ph.D.	5/3/213
Product Quality Reviewer(s)	Date
SUSAN L. KIRSHNER, Ph.D.	5/3/213
Branch Chief/Team Leader/Supervisor	Date
AMY ROSENBERG, M.D., Ph.D.	5/3/213
Division Director	Date

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/s/

LAURA I SALAZAR FONTANA
05/06/2013

SUSAN L KIRSHNER
05/06/2013

AMY S ROSENBERG
05/06/2013

PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & OMPQ)

BLA/NDA Number:	Applicant:	Stamp Date:
125390\0\18	Amylin Pharmaceuticals, LLC	March 27, 2013
Established/Proper Name: Metreleptin	**BLA/NDA Type:** Original	

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed ❑ including list of all establishment sites and their registration numbers	Y Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y Y N Y Y N Y Y Y Y N Y N Y N Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include: ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable (e.g. conforms to published guidance)	Y Y Y Y Y Y Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

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CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
❑ Drug Substance	Y	
❑ Drug Product	Y	
❑ Facilities and Equipment	Y	
❑ Adventitious Agents Safety Evaluation	Y	OBP Lead
❑ Novel Excipients	N	Drug product contains no novel excipients.
❑ Executed Batch Records	Y	
❑ Method Validation Package	Y N	OBP Lead
❑ Comparability Protocols	Y N	OBP Lead

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
❑ general info	Y	
o nomenclature		
o structure (e.g. sequence, glycosylation sites)		
o properties		
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control	Y	
o batch numbering and pooling scheme		
o cell culture and harvest		
o purification		
o filling, storage and shipping		
❑ control of materials	Y N	OBP Lead
o raw materials and reagents		
o biological source and starting materials		
o cell substrate: source, history, and generation		
o cell banking system, characterization, and testing		
❑ control of critical steps and intermediates	Y	
o justification of specifications		
o stability		

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ process validation (prospective plan, results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	OBP Lead
❑ characterization of drug substance		
❑ control of drug substance		
o specifications		
o justification of specs.	Y	
o analytical procedures	Y	
o analytical method validation		
o batch analyses		
❑ reference standards	Y N	OBP Lead
❑ container closure system	Y	
❑ stability		
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval	Y	
o protocol		
o results		
o method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
o preservative effectiveness	N	
o container-closure integrity	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ batch formula	Y	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y	
❑ controls of critical steps and intermediates	Y	
❑ process validation including aseptic processing & sterility assurance:	Y	
o Filter validation		
o Component, container, closure depyrogenation	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
and sterilization validation o Validation of aseptic processing (media simulations) o Environmental Monitoring Program o Lyophilizer validation o Other needed validation data (hold times)	Y Y Y Y	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y N	OBP Lead
❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	
❑ reference standards or materials	Y N	OBP Lead
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF & LOAs o administration device(s)	Y	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y	
Diluent (vials or filled syringes) [3.2P′]		Lyophilized product is to be reconstituted with WFI or bacteriostatic WFI. The diluent is not provided with product.
❑ description and composition of diluent	N	
❑ pharmaceutical development o preservative effectiveness o container-closure integrity	N N	N/A. Diluent not provided. N/A. Diluent not provided.
❑ manufacturers (names, locations, and responsibilities of all sites involved)	N	N/A. Diluent not provided.
❑ batch formula	N	N/A. Diluent not provided.
❑ description of manufacturing process for production through	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)		
❑ controls of critical steps and intermediates	N	N/A. Diluent not provided.
❑ process validation including aseptic processing & sterility assurance:	N	N/A. Diluent not provided.
o Filter validation	N	N/A. Diluent not provided.
o Component, container, closure depyrogenation and sterilization validation	N	N/A. Diluent not provided.
o Validation of aseptic processing (media simulations)	N	N/A. Diluent not provided.
o Environmental Monitoring Program	N	N/A. Diluent not provided.
o Lyophilizer sterilization validation	N	N/A. Diluent not provided.
o Other needed validation data (hold times)		
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	N	N/A. Diluent not provided.
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	N	
❑ reference standards	N	
❑ container closure system	N	
o specifications (vial, elastomer, drawings)		
o availability of DMF & LOAs		
❑ stability	N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
Other components to be marketed (full description and supporting data, as listed above):		Product does not include other components.
❑ other devices	Y N	Not applicable
❑ other marketed chemicals (e.g. part	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
of kit)		
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y Y N	OBP Lead OBP Lead
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	Y Y N Y N	OBP Lead OBP Lead OBP Lead
Literature references and copies [3.3]	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	OBP Lead
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	OBP Lead
Data demonstrating comparability of	Y N	OBP Lead

Examples of Filing Issues	Yes?	If not, justification, action & status
product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)		
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	OBP Lead
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	Y Y Y Y	 OBP Lead
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	OBP Lead
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

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IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kalavati Suvarna, Ph.D. Date
Drug Substance Microbiology Reviewer
OC/OMPQ/DGMPA/BMAB

Steven Fong, Ph.D. Date
Drug Product Microbiology Reviewer
OC/OMPQ/DGMPA/BMAB

Patricia Hughes, Ph.D. Date
Team Leader
OC/OMPQ/DGMPA/BMAB

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

/s/

KALAVATI C SUVARNA
04/30/2013

STEVEN FONG
04/30/2013

PATRICIA F HUGHES TROOST
04/30/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: October 3, 2012

Applicant Name: Amylin Pharmaceuticals
U.S. License #: 1854
STN(s): 125390
Product(s): Metreleptin
Short summary of application: Original BLA – Initial TB-EER request

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FACILITY INFORMATION

Manufacturing Location:
Firm Name: Sandoz GmbH (Sandoz)
Address: Biochemiestrasse 10, Kundl,Tyrol A-6250, Austria
FEI: 3002806523
Short summary of manufacturing activities performed: Drug substance manufacturing

Inspected by IOG from 07/19/2010 – 7/29/10 and classified VAI. This CGMP inspection found the (b) (4) profiles updated and acceptable.

Manufacturing Location:
Firm Name: Amylin Pharmaceuticals, Inc.
Address: 9360 Towne Centre Drive, San Diego, CA 92121
FEI: 1000519848

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[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Short summary of manufacturing activities performed: Release and stability testing of drug substance and drug product

Inspected by LOS-DO from 12/13/11-12/21/11 and classified NAI. This CGMP inspection found the CTL profile updated and acceptable.

Manufacturing Location:
(b) (4)

Short summary of manufacturing activities performed: release testing of drug substance

Inspected by (b) (4) and classified NAI. This CGMP inspection covered controlled testing operations and found the CTL profile updated and acceptable.

Manufacturing Location:
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Drug product manufacturing and release testing

Inspected by (b) (4) and classified VAI. This CGMP inspection covered sterile processing operations and found them acceptable. The (b) (4) profile was updated and acceptable.

Manufacturing Location:
(b) (4)

Short summary of manufacturing activities performed: Stability testing

Inspected by (b) (4) and classified VAI. This CGMP inspection covered controlled testing operations and found the CTL profile updated and acceptable.

OVERALL RECOMMENDATION:

There are no pending or ongoing compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 15-30 days prior to the planned action date.

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

/s/

MAHESH R RAMANADHAM
04/30/2012