

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125390Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 24, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Subject: Evaluation of proposed REMS - Final review

Drug Name(s): Myalept (metreleptin)

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company (BMS)/AstraZeneca /  
Amylin

OSE RCM #: 2013-821

## 1 INTRODUCTION

This review documents DRISK's final evaluation of the proposed risk evaluation and mitigation strategy (REMS) for metreleptin BLA 125390 initially received March 27, 2013 and submitted via email on February 23 and 24, 2014.

## 2 MATERIALS REVIEWED

- Proposed REMS. Submitted via email February 23 (Introductory Information sheet) and 24, 2014 (REMS Document, Prescriber Enrolment Form, Prescription Authorization Form, Prescriber Training Module, REMS webpage, and Supporting Document)
- Madara P. General Advice Letter signed in DARRTS on February 24, 2014 by Madara P.
  - This documents agreement with the REMS and materials as submitted via email on February 24, 2014. On Page 8, Dr. Kinnari Patel notes previous agreement with the Introduction Information Sheet.

### **DRISK reviews related to the February 23, 2014 email submission**

- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 24, 2014 by Robottom S and LaCivita C.
  - Comments on and revisions to the REMS document, REMS materials and REMS Supporting Document sent via email on February 23, 2014.

### **DRISK reviews related to the February 20, 2014 email submission**

- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 24, 2014 by Robottom S and LaCivita C.
  - Comments on and revisions to the REMS document, REMS materials and REMS Supporting Document sent via email on February 21 and 23, 2014.

### **Other DRISK reviews related to the March 27, 2013 submission**

- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 19, 2014 by Robottom S and LaCivita C.
  - This review comments on the *Myalept REMS Prescriber Training Module*.
- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 14, 2014 by Robottom S and LaCivita C.
  - This review comments on and provides revisions to the REMS Document, Introductory Information Sheet titled *Myalept REMS Program: An Introduction*, REMS website, and REMS Assessment.
- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 5, 2014 by Robottom S and Manzo C.

- This review provided comments on the REMS proposal and revisions to Prescriber Enrollment Form and Prescription Authorization Form
- Robottom S. DRISK REMS Options review for BLA 125390. Signed in DARRTS on November 26, 2013 by Robottom S and Manzo C.

### **3 RECOMMENDATION**

The proposed REMS and Supporting Document submitted on February 23 and 24, 2014 incorporates the comments DMEP and DRISK conveyed in the previous reviews and via email.

DRISK finds the REMS and REMS Supporting Document to be acceptable. DRISK recommends approval of the Myalept REMS.

### **ATTACHMENTS**

- REMS Document
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction*
- *Prescriber Training Module*
- Myalept REMS website

**Initial REMS Approval: [02/2014]**

**BLA 125390**  
**MYALEPT™ (metreleptin)**

Drug Class: Recombinant human leptin analog

Amylin Pharmaceuticals LLC  
9625 Towne Centre Drive  
San Diego, CA 92121  
1-800-236-9933

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOALS**

The goal of the MYALEPT REMS is to mitigate (1) the risks of serious adverse sequelae (such as severe infections, excessive weight gain, glucose intolerance, diabetes mellitus) due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT, and (2) the risk of lymphoma by:

- Educating prescribers about the development of neutralizing anti-metreleptin antibodies, the serious adverse sequelae that may result from these antibodies, and the risk for lymphoma associated with MYALEPT
- Limiting the population exposed to MYALEPT by requiring prescriber certification, pharmacy certification, and prescriber attestation that each patient has with a diagnosis consistent with the approved indication

## II. REMS ELEMENTS

### A. Elements to Assure Safe Use (ETASU)

1. **Healthcare Providers (HCPs) who prescribe MYALEPT are specially certified.**
  - a. Amylin will ensure that HCPs who prescribe MYALEPT are specially certified.
  - b. To become specially certified to prescribe MYALEPT, prescribers must enroll in the MYALEPT REMS Program. Prescribers must complete the following requirements:
    - i. review the Prescribing Information
    - ii. complete the Prescriber Training Module
    - iii. complete and sign the *Prescriber Enrollment Form* and submit it to the MYALEPT REMS Program.
  - c. Amylin will:
    - i. Ensure that the *Prescriber Training Module* and the *Prescriber Enrollment Form* are available on the MYALEPT REMS Program website ([www.MYALEPTREMS.com](http://www.MYALEPTREMS.com)) or can be obtained by contacting the MYALEPT REMS Program by phone at 1-855-6MYALEPT.
    - ii. Ensure that prescribers complete the *Prescriber Training Module* and the *Prescriber Enrollment Form* before activating prescribers' certification in the MYALEPT REMS Program.
    - iii. Ensure that prescribers are notified when they have been successfully certified by the MYALEPT REMS Program.
    - iv. Inform certified prescribers following substantial changes to the MYALEPT REMS or MYALEPT REMS Program; substantial changes include significant changes to the operation of the MYALEPT REMS Program or changes to the Prescribing Information that affect the risk-benefit profile of MYALEPT.
    - v. Communicate information about the risks and MYALEPT REMS Program requirements to prescribers through the MYALEPT REMS Program website and MYALEPT REMS introductory information sheet titled *MYALEPT REMS Program: An Introduction*. Amylin will provide the *REMS Program: An Introduction, Prescriber Training Module, Prescriber Enrollment Form*, and the Prescribing Information to prescribers who (1) attempt to prescribe MYALEPT and are not yet certified, or (2) inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Training Module*
- *Prescriber Enrollment Form*
- *MYALEPT REMS Program: An Introduction*
- *MYALEPT REMS Program website*

**2. Pharmacies that dispense MYALEPT are specially certified.**

- a. Amylin will ensure that MYALEPT is dispensed only by specially certified pharmacies.

To become certified to dispense MYALEPT, each pharmacy representative must agree to the following:

- i. to educate all pharmacy staff involved in the dispensing of MYALEPT on the MYALEPT REMS Program requirements
- ii. to put processes and procedures in place to verify, prior to dispensing MYALEPT, that:
  - 1) the prescriber is certified in the MYALEPT REMS Program
  - 2) the *MYALEPT REMS Prescription Authorization Form* is received for each new prescription
- iii. to be audited to ensure that all processes and procedures are in place and are being followed for the MYALEPT REMS Program
- iv. to provide prescription data to the MYALEPT REMS Program, and
- v. to refrain from reselling or transferring MYALEPT to other pharmacies or distributors.

The following material is part of the REMS and appended:

- *MYALEPT REMS Prescription Authorization Form*

- 3. MYALEPT is dispensed only to patients with evidence or other documentation of safe-use conditions.**
- a. MYALEPT is dispensed only to patients whose prescribers are specially certified in the MYALEPT REMS Program and attest on the MYALEPT REMS Prescription Authorization Form that:
- i. They understand that MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.
  - ii. They affirm that their patient has a clinical diagnosis consistent with the approved indication, and that the patient (or caregiver) has been properly informed of the benefits and risks of MYALEPT therapy.
  - iii. They understand that MYALEPT is not indicated for the treatment of complications of partial lipodystrophy.
  - iv. They understand that MYALEPT is not indicated for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH).
  - v. They understand that MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.
  - vi. They understand that MYALEPT is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.
  - vii. They understand that MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.
  - viii. They understand that MYALEPT is associated with serious adverse events due to the development of anti-metroleptin antibodies that neutralize endogenous leptin and/or Myalept
  - ix. They agree to test for neutralizing antibodies to MYALEPT if a patient experiences severe infections or if they suspect MYALEPT treatment is no longer working (e.g., loss of glycemic control, increased triglycerides).
  - x. They understand that MYALEPT is associated with a risk of lymphoma.



- xi. They understand it is important to carefully consider treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy

## **B. Implementation System**

1. Amylin will ensure that MYALEPT is distributed to and dispensed only by certified pharmacies.
2. Amylin will maintain, monitor, and evaluate the implementation of the MYALEPT REMS Program.
  - a. Amylin will maintain a secure, validated database of certified prescribers and pharmacies in the MYALEPT REMS Program. Amylin will send confirmation of certification to each certified pharmacy.
  - b. Amylin will maintain a MYALEPT REMS Program Call Center to support patients, prescribers, and pharmacies interfacing with the MYALEPT REMS.
  - c. Amylin will ensure that all materials listed in or appended to the MYALEPT REMS Program will be available through the MYALEPT REMS Program website ([www.MYALEPTREMS.com](http://www.MYALEPTREMS.com)) or by calling the MYALEPT REMS Program Call Center at 1-855-6MYALEPT.
  - d. If there are substantive changes to the MYALEPT REMS or MYALEPT REMS Program, Amylin will update all affected materials, and notify enrolled prescribers and certified pharmacies, as applicable. Substantive changes are defined as significant changes to the operation of the MYALEPT REMS Program or changes to the Prescribing Information that affect the risk-benefit profile of MYALEPT.
  - e. Amylin will monitor and audit the certified pharmacies within 180 days after the pharmacy is certified to ensure that all processes and procedures are in place and functioning to support the requirements of the MYALEPT REMS Program. Thereafter, Amylin will include the certified pharmacies in the company's annual audit plan. Corrective action will be instituted by Amylin if noncompliance is found.
  - f. Based on monitoring and evaluation of the MYALEPT REMS elements to assure safe use, Amylin will take reasonable steps to improve implementation of these elements and to maintain compliance with the MYALEPT REMS Program requirements, as applicable.

### **C. Timetable for Submission of Assessments**

Amylin will submit REMS Assessments to the FDA 6 months, 12 months, and annually thereafter from the date of the initial REMS approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amylin will submit each assessment so that it will be received by the FDA on or before the due date.



11.3 mg per vial

## MYALEPT™ REMS Program Prescriber Enrollment Form

MYALEPT will be available only through the MYALEPT REMS Program. To prescribe MYALEPT, a prescriber must: (1) review the Prescribing Information, review and complete the Prescriber Training Module, (2) complete this one-time MYALEPT REMS Program Prescriber Enrollment Form, and (3) complete and submit a MYALEPT REMS Prescription Authorization Form for each new prescription.

Complete this enrollment form and fax it to the MYALEPT REMS Program at 1-877-328-9682.

Prescriber Information (Please Print *indicates a required field.)			
Full Name (first, middle, last)*			
Credentials*			
<input type="checkbox"/> MD <input type="checkbox"/> DO <input type="checkbox"/> NP <input type="checkbox"/> PA <input type="checkbox"/> Other (specify) _____			
Physician Specialty*			
<input type="checkbox"/> Endocrinology <input type="checkbox"/> Family Medicine <input type="checkbox"/> Cardiology <input type="checkbox"/> General Internal Medicine <input type="checkbox"/> Pediatrics <input type="checkbox"/> Other _____			
Who do you treat?			
<input type="checkbox"/> Adults <input type="checkbox"/> Pediatrics <input type="checkbox"/> Both			
Practice / Facility Name			
Address 1*			
Address 2 (optional)		City*	State*
Address 2 (optional)		City*	State*
Address 2 (optional)		City*	State*
Address 2 (optional)		City*	State*
Phone number*	Alternate phone number*	Fax number*	
Email*	NPI #*		
Office Contact			
Full Name (first, middle, last)*			
Phone number (if different from above)	Fax number (if different from above)	Email* (if office contact is provided)	

**Prescriber Attestation. By completing this form, I attest that:**

- I understand that MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin-deficiency in patients with congenital or acquired generalized lipodystrophy.
- I understand that MYALEPT is available only through the MYALEPT REMS Program and that I must comply with the program requirements in order to prescribe MYALEPT.
- I have completed the MYALEPT REMS Prescriber Training Module.
- I understand that MYALEPT is associated with serious adverse events due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT.
- I agree to test for neutralizing antibodies in patients who experience severe infections or if I suspect MYALEPT is no longer working (e.g., loss of glycemic control, or increases in triglycerides).
- I understand that MYALEPT is associated with a risk of lymphoma.
- I will carefully consider the risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy.
- I understand that MYALEPT is not indicated for the treatment of complications of partial lipodystrophy.
- I understand that MYALEPT is not indicated for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH).
- I understand that MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.
- I understand that MYALEPT is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia without concurrent evidence of congenital or acquired generalized lipodystrophy.
- I understand that MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.
- I agree that personnel from the MYALEPT REMS Program may contact me to gather further information or resolve discrepancies or to provide other information related to MYALEPT or the MYALEPT REMS Program.
- I will complete and submit a MYALEPT REMS Program Prescription Authorization Form for each new prescription.
- I agree that Amylin, its agents and contractors such as the pharmacy providers, may contact me via phone, mail, or email to survey me on the effectiveness of the program requirements for the MYALEPT REMS Program.

Signature\* \_\_\_\_\_

Date\* \_\_\_\_\_

**If you have any questions, please contact the MYALEPT REMS Program.**

Phone number: 1-855-669-2537 | Fax number: 1-877-328-9682 | www.MYALEPTREMS.COM

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11.3 mg per vial

## MYALEPT™ REMS Program Prescription Authorization Form

**Instructions:** Complete this form for each new prescription. All fields are required. Please Print.

**Please FAX completed form to MYALEPT REMS Program at 1-877-328-9682.** This prescription is only valid if received by fax.

For New York prescribers: In addition to this completed form, provide New York specific prescription blanks.

Patient Information			
Full Name (first, middle, last)		Gender <input type="checkbox"/> Male <input type="checkbox"/> Female	Date of Birth
Address		City	State ZIP code
Preferred phone number	Alternate phone number	Preferred time to contact: (check one) <input type="checkbox"/> Day <input type="checkbox"/> Evening	
Email		Alternate contact/phone #	
Shipping Information			
Full Name (first, middle, last)			
Address (if different from above)		City	State ZIP code
Send initial shipment to prescribing doctor's office <input type="checkbox"/> Yes <input type="checkbox"/> No			
Prescriber Information			
Full Name (first, middle, last)			
Practice / Facility Name		Office Contact Person	
Address 1			
Address 2		City	State ZIP code
Office Phone number	Office Fax number	License #	NPI #
MYALEPT Prescription			
<b>Starting Dose:</b> [ ] .06 mg/kg [ ] 2.5 mg [ ] 5 mg [ ] <b>Maintenance Dose:</b> _____			
Patient Weight	Days supply	Refills #	
Directions (e.g., by subcutaneous injection once daily)			
List or Attach a List of Concomitant Medications		Allergies	

**Attestation of REMS Requirements. By completing this form, I attest that:**

- I understand that MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin-deficiency in patients with congenital or acquired generalized lipodystrophy.
- I affirm that my patient has a clinical diagnosis consistent with generalized lipodystrophy, and that my patient (or their caregiver) has been properly informed of the benefits and risks of MYALEPT therapy.
- I understand that MYALEPT is not indicated for the treatment of complications of partial lipodystrophy.
- I understand that MYALEPT is not indicated for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH).
- I understand that MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.
- I understand that MYALEPT is not indicated for use in patients with metabolic disease including diabetes mellitus and hypertriglyceridemia without concurrent evidence of congenital or acquired generalized lipodystrophy.
- I understand that MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.
- I understand that MYALEPT is associated with serious adverse events due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT.
- I agree to test for neutralizing antibodies in patients who experience severe infections or if I suspect MYALEPT is no longer working (e.g., loss of glycemic control, or increases in triglycerides).
- I understand that MYALEPT is associated with a risk of lymphoma.
- I understand I must carefully consider the risks of treatment with MYALEPT in patients with significant hematological abnormalities and/or acquired generalized lipodystrophy.

**Physician Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_



**myalept**<sup>TM</sup>  
**(metreleptin) For Injection**

**11.3 mg per vial**

**Risk Evaluation and Mitigation Strategy (REMS) Program**  
**Prescriber Training Module**

# Contents



- Introduction
- MYALEPT™ (metreleptin) for injection Product Information
  - **Boxed Warning:** risk of development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT
  - **Boxed Warning:** risk of lymphoma
  - Appropriate patient selection
- MYALEPT REMS Program Information
- Knowledge Assessment



# Introduction

# Introduction



**MYALEPT™ (metreleptin) for injection is available only through a restricted program called the MYALEPT REMS Program.**

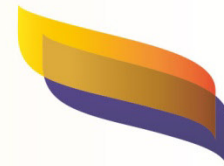
- Prescribers must complete this training module and enroll in the MYALEPT REMS Program prior to prescribing MYALEPT.

**The purpose of this training module is to educate prescribers about**

- the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the serious adverse events that may result from these antibodies,
- the risk of lymphoma, and
- appropriate patient selection

**Because of these risks, appropriate patient selection consistent with the approved indication for MYALEPT is very important.**





# **MYALEPT™ (metreleptin) for injection Product Information**

# Indication



**MYALEPT™ (metreleptin) for injection is indicated** as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired **generalized lipodystrophy**

# Serious Risks Associated with MYALEPT



## Serious Risks Associated with MYALEPT

1. Development of anti-metrelleptin antibodies that neutralize endogenous leptin and MYALEPT
2. Lymphoma

# Boxed Warning: Anti-metresleptin Antibodies with Neutralizing Activity - Serious Adverse Events



- Anti-metresleptin antibodies with neutralizing activity associated with adverse events consistent with loss of endogenous leptin activity and/or loss of efficacy have been identified among patients with generalized lipodystrophy
  - 2 of 33 patients who underwent antibody testing
    1. tested positive for anti-metresleptin antibodies with neutralizing activity  
**and**
    2. reported adverse events consistent with neutralizing activity, including severe infections, loss of glycemic control, and increases in triglycerides

# Boxed Warning: Anti-metresleptin Antibodies with Neutralizing Activity - Serious Adverse Events (continued)



## ■ In other populations

- 3 of 563 patients who underwent antibody testing
  1. tested positive for anti-metresleptin antibodies with neutralizing activity  
**and**
  2. reported adverse events consistent with neutralizing activity, including excessive weight gain and development of glucose intolerance or diabetes mellitus

The clinical implications associated with development of anti-metresleptin antibodies with neutralizing activity are not well-characterized at this time due to the small number of reports.

# Antibody Testing in MYALEPT Trials - Data



- Anti-metresleptin antibodies were detected in 84% (36/43) of patients with generalized lipodystrophy studied in the MYALEPT trials
- Total anti-metresleptin antibody titers ranged between 1:5 and 1:1,953,125
- Anti-metresleptin antibodies with neutralizing activity associated with adverse events consistent with loss of endogenous leptin activity and/or loss of MYALEPT efficacy were observed in 6% (2/33) of the patients tested

# Antibody Testing in MYALEPT Trials - Limitations



- The immunogenicity assays utilized in clinical trials lacked sensitivity, resulting in potential underestimation of the number of samples positive for anti-metresatptin antibodies with neutralizing activity
  - The observed incidence of an antibody assay (including neutralizing antibody assays) positivity may be influenced by several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

# Antibody Testing in MYALEPT Trials – Limitations (continued)



- Antibody testing was not performed uniformly in the MYALEPT trials. The incompleteness of the current immunogenicity database precludes understanding of the magnitude and persistence of the observed anti-metrelleptin antibody responses.
- Comparison of the incidence of antibodies to metrelleptin with the incidence of antibodies to other products may be misleading.



# Neutralizing Activity - What is My Role?



- Test for neutralizing activity in patients who experience severe infections or if you suspect that MYALEPT is no longer working.
- Contact Amylin at 1-866-216-1526 for instructions on how to submit samples for neutralizing antibody testing. The assay is not commercially available.

Amylin will ask you to:

1. Obtain written consent from your patient to release the sample and send a copy of the consent to Amylin.
2. Complete a questionnaire to explain why you are requesting neutralizing activity testing and send it to Amylin.
3. Send the sample to the designated laboratory for testing.
  - The results are generally available within 60 days
4. Amylin will contact you to provide and discuss the results.

# Boxed Warning: Lymphoma



- Three cases of T-cell lymphoma have been reported in the MYALEPT lipodystrophy program
  - All 3 patients had **acquired generalized lipodystrophy (out of a total of 20 patients with acquired generalized lipodystrophy)**.
    - Two of these patients were diagnosed with peripheral T-cell lymphoma while receiving MYALEPT.
    - Both had immunodeficiency and significant hematologic abnormalities, including severe bone marrow abnormalities, before the start of MYALEPT treatment.
    - A separate case of anaplastic large cell lymphoma was reported in a patient receiving MYALEPT who did not have hematological abnormalities before treatment.

# Lymphoma – What is My Role?



- Take a careful medical history for past or current hematologic abnormalities
- Carefully consider the benefits and risks of treatment with MYALEPT in patients with
  - significant hematologic abnormalities, and/or
  - acquired generalized lipodystrophy

# Adverse Reaction Reporting



**To report SERIOUS ADVERSE REACTIONS, please call/contact:**

- 1-855-669-2537 and/or
- FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)



# Appropriate Patient Selection

# Appropriate Patient Selection



## Contraindication – General Obesity

MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.

- MYALEPT has not been shown to be effective in treating general obesity, and the development of anti-metreleptin antibodies with neutralizing activity has been reported in obese patients treated with MYALEPT
- Adverse events consistent with loss of endogenous leptin activity have been identified in three patients without lipodystrophy who received metreleptin (excessive weight gain, development of glucose intolerance or diabetes mellitus).

The clinical implications associated with development of anti-metreleptin antibodies with neutralizing activity are not well-characterized at this time due to the small number of reports.



## Important Limitations of Use

- **The safety and effectiveness of MYALEPT for the following conditions have not been established**
  - The treatment of complications of partial lipodystrophy
  - The treatment of liver disease including non-alcoholic steatohepatitis (NASH)
  
- **MYALEPT is not indicated for use in patients with**
  - HIV-related lipodystrophy
  - Metabolic disease including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.



# **MYALEPT™ (metreleptin) for injection**

## **REMS PROGRAM INFORMATION**



# MYALEPT™ (metreleptin) for injection

## REMS Program



### Key program elements:

- Certification of Prescribers of MYALEPT
  - Certification consists of training, and enrolling in the MYALEPT REMS Program.
- Completion of a Prescription Authorization Form for each new prescription
- Restricted distribution of MYALEPT through certified pharmacies.

# MYALEPT™ (metreleptin) for injection

## REMS Program



**Before prescribing MYALEPT, prescribers must complete the following steps:**

1. Review the Prescribing Information and this Prescriber Training Module.
2. Complete, sign, and submit the one-time MYALEPT REMS Program Prescriber Enrollment Form.
3. Complete, sign, and submit the MYALEPT REMS Program Prescription Authorization Form for each new prescription.

Note: All Materials can be downloaded from the MYALEPT REMS website at:  
[www.MYALEPTREMS.com](http://www.MYALEPTREMS.com)

Or request these materials by calling 1-855-669-2537

# 1. Review Prescriber Education Materials



Review the following Prescriber Education Materials:

- a) MYALEPT™ (metreleptin) for injection Prescribing Information
- b) This Prescriber Training Module

## 2. Enroll in MYALEPT™ (metreleptin) for injection REMS Program



To enroll in the MYALEPT REMS Program:

- Download the MYALEPT REMS Program Prescriber Enrollment Form at [www.MYALEPTREMS.com](http://www.MYALEPTREMS.com) or request a copy by calling 1-855-669-2537
- Complete the enrollment form
- Sign & submit the enrollment form
  - Fax to 1-877-328-9682

# 3. Submit Prescription Authorization Form



**When prescribing MYALEPT™ (metreleptin) for injection, a prescriber must complete a Prescription Authorization Form for each new prescription.**

As part of completing the Prescription Authorization Form, you attest that:

- I understand that MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin-deficiency in patients with congenital or acquired generalized lipodystrophy.
- I affirm that my patient has a clinical diagnosis consistent with generalized lipodystrophy, and that my patient (or their caregiver) has been properly informed of the benefits and risks of MYALEPT therapy.

# 3. Submit Prescription Authorization Form (continued)



- I understand that MYALEPT is not indicated for the treatment of complications of partial lipodystrophy.
- I understand that MYALEPT is not indicated for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH).
- I understand that MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.
- I understand that MYALEPT is not indicated for use in patients with metabolic disease including diabetes mellitus and hypertriglyceridemia without concurrent evidence of congenital or acquired generalized lipodystrophy.

# 3. Submit Prescription Authorization Form (continued)



- I understand that MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.
- I understand that MYALEPT is associated with serious adverse events due to the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT.
- I agree to test for neutralizing antibodies in patients who experience severe infections or if I suspect MYALEPT is no longer working (e.g., loss of glycemic control, or increases in triglycerides).
- I understand that MYALEPT is associated with a risk of lymphoma.
- I understand I must carefully consider the risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy.

# 3. Submit Prescription Authorization Form



**Each new prescription for MYALEPT must be written using the MYALEPT Prescription Authorization Form.**

1. Download the Prescription Authorization Form at [www.MYALEPTREMS.com](http://www.MYALEPTREMS.com) or request a copy by calling 1-855-669-2537
2. Complete the Prescription Authorization Form
3. Sign & submit the Prescription Authorization Form
  - Fax to 1-877-328-9682





# Knowledge Assessment

# Knowledge Assessment



- The following questions about MYALEPT™ (metreleptin) for injection are provided to reinforce learning.
- If you have difficulty answering these questions, review the previous slides and refer to the Prescribing Information.

# Knowledge Assessment



1. Which of the following statements is true?
  - MYALEPT (metreleptin) for injection is indicated for use in patients with HIV-related lipodystrophy.
  - MYALEPT is indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of inherited or acquired generalized lipodystrophy.
  - MYALEPT is a recombinant analog of murine leptin.
  - MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

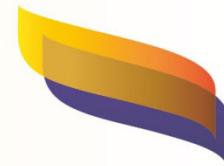
# Knowledge Assessment



1. Which of the following statements is true?
- MYALEPT (metreleptin) is indicated for use in patients with HIV-related lipodystrophy.
  - MYALEPT is indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of inherited or acquired generalized lipodystrophy.
  - MYALEPT is a recombinant analog of murine leptin.
  - MYALEPT is indicated** as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

Answer: MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy

*(continued on next slide)*



*(continued from previous slide)*

- **The safety and effectiveness of MYALEPT for the following conditions have not been established**
  - The treatment of complications of partial lipodystrophy
  - The treatment of liver disease including non-alcoholic steatohepatitis (NASH)
  
- **MYALEPT is not indicated for use in patients with**
  - HIV-related lipodystrophy
  - Metabolic disease including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.
  
- **MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency.**

# Knowledge Assessment



2. The risks and benefits of MYALEPT™ (metreleptin) for injection treatment should be carefully considered in patients with significant hematologic abnormalities (for example, leukopenia, neutropenia, bone marrow abnormalities, lymphoma and/or lymphadenopathy) and/or acquired generalized lipodystrophy.

True

False

# Knowledge Assessment



2. The risks and benefits of MYALEPT™ (metreleptin) for injection treatment should be carefully considered in patients with significant hematologic abnormalities (for example, leukopenia, neutropenia, bone marrow abnormalities, lymphoma and/or lymphadenopathy) and/or acquired generalized lipodystrophy.

True

False

Answer: 

- Peripheral T-cell lymphoma was diagnosed in two patients with acquired generalized lipodystrophy while receiving MYALEPT.

- Both had immunodeficiency and significant hematologic abnormalities including severe bone marrow abnormalities before the start of MYALEPT treatment.

- A separate case of anaplastic large cell lymphoma was reported in a patient with acquired generalized lipodystrophy who did not have hematologic abnormalities before MYALEPT treatment.

# Knowledge Assessment



3. Developing neutralizing activity to metreleptin could:
- affect endogenous leptin
  - result in loss of efficacy
  - both of the above
  - none of the above



# Knowledge Assessment



3. Developing neutralizing activity to metreleptin could:

affect endogenous leptin

result in loss of efficacy

both of the above

none of the above

Answer: Developing neutralizing activity to metreleptin could affect endogenous leptin and could result in loss of efficacy.

# Knowledge Assessment



4. If a patient is experiencing severe infections and/or I suspect Myalept is no longer working, I will contact Amylin for instructions on how to send a blood sample to test for anti-metreleptin antibodies with neutralizing activity.
- True
  - False

# Knowledge Assessment



4. If a patient is experiencing severe infections and/or I suspect Myalept is no longer working, I will contact Amylin for instructions on how to send a blood sample to test for anti-metreleptin antibodies with neutralizing activity.

True

False

Answer: If you suspect your patient is experiencing complications from the development of anti-metreleptin neutralizing antibodies, you can submit a request and obtain results from Amylin at no cost.

1. Call 1-866-216-1526
  - Amylin will provide you information on the requirements for sample collection and shipment.
2. Amylin will instruct you to:
  - a. Obtain written consent from your patient to release the sample and send a copy of the consent to Amylin.
  - b. Complete a questionnaire to explain why you are requesting neutralizing activity testing.
  - c. Send the sample and paperwork to the designated laboratory for testing.
    - The results are generally available within 60 days
3. Amylin will contact you to provide and discuss the results.

# Knowledge Assessment



5. How often should the Prescription Authorization Form be completed?
- Each new prescription
  - Only on the first prescription
  - Every refill
  - Once a year

# Knowledge Assessment



5. How often should the Prescription Authorization Form be completed?
- ✓ Each new prescription
  - Only on the first prescription
  - Every refill
  - Once a year

Answer: For each new prescription, the prescriber must submit a Prescription Authorization Form.

# Knowledge Assessment



6. MYALEPT™ (metreleptin) for injection is available only through certified pharmacies.
- True
  - False

# Knowledge Assessment



6. MYALEPT™ (metreleptin) for injection is available only through certified pharmacies.
- True
- False

Answer: MYALEPT is available only through pharmacies that are specially certified and agree to follow REMS requirements. For a list of certified pharmacies call: 1-855-669-2537.

# Completion of Training for the MYALEPT™ (metreleptin) for injection REMS Program



**You have completed training for the MYALEPT REMS Program.**

To enroll in the MYALEPT REMS Program, complete the Enrollment Form and return via fax at 1-877-328-9682.

For more information on the MYALEPT REMS Program, please call 1-855-669-2537 or visit [www.MYALEPTREMS.com](http://www.MYALEPTREMS.com).

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## MYALEPT REMS Program: An Introduction

### What is the MYALEPT REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS is a strategy to manage known or potential risks associated with a drug, and is required by the FDA to ensure that the benefits of the drug outweigh its risks. MYALEPT is available only under a restricted program called the MYALEPT REMS Program because of:

- the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the serious adverse events that may result
- the risk of lymphoma.

**Because of these risks, appropriate patient selection consistent with the approved indication for MYALEPT is very important.**

### MYALEPT REMS Program Requirements

- Certification of Prescribers of MYALEPT
- Completion of a Prescription Authorization Form for each new prescription
- Restricted distribution of MYALEPT through certified pharmacies

### Certification of Prescribers of MYALEPT

1. Review the Prescribing Information and MYALEPT Prescriber Training Module
2. Complete, sign, and submit the one-time MYALEPT REMS Program Prescriber Enrollment Form

All Materials can be downloaded from the MYALEPT REMS website at: [www.MYALEPTREMS.com](http://www.MYALEPTREMS.com).  
Or request these materials by calling 1-855-669-2537.

### Completion of Prescription Authorization Form

**Each new prescription for MYALEPT must be written using the MYALEPT Prescription Authorization Form.**

- Download the Prescription Authorization Form at [www.MYALEPTREMS.com](http://www.MYALEPTREMS.com) or request a copy by calling 1-855-669-2537
- Complete the Prescription Authorization Form

### Restricted Distribution of MYALEPT through Certified Pharmacies

Prescription Authorization Form must be signed and submitted by:  
Fax to 1-877-328-9682

Myalept REMS page

MYALEPT™ (metreleptin) for injection

http://www.myaleptrems.com

U.S. Full Prescribing Information | Medication Guide | Important Safety Information

This site is for U.S. Healthcare Professionals only.

**You are about to leave the MYALEPT (metreleptin) for injection Web Site**

Use of and access to this information is subject to the terms, limitations, and conditions set by the Web site and/or database producer.

**CLOSE** **CONTINUE**

**Program Requirements**

MYALEPT is available only through the MYALEPT REMS Program. The MYALEPT REMS Program requirements include:

**For Prescribers:**

- **Certification** of prescribers of MYALEPT
  - Certification consists of completion of **training, and enrollment** in the MYALEPT REMS Program
- **Completion** of a Prescription Authorization form for **each** new prescription

Find out more about [Training & Enrollment](#).

**For Pharmacies:**

- **Restricted distribution** of MYALEPT to patients with completed Prescription Authorization Forms from prescribers who are certified in the MYALEPT REMS Program

**Training & Enrollment**

Healthcare providers who prescribe MYALEPT must review the prescriber training materials to enroll in the MYALEPT REMS Program.

**Steps to Prescriber Certification**

1. **Review the Prescriber Education Materials**
  - [MYALEPT Prescribing Information](#)
  - [Prescriber Training Module](#)
2. **Complete and submit the MYALEPT REMS Program Prescriber Enrollment Form**
  - Print and sign the [Prescriber Enrollment Form](#) or request a copy by calling 1-855-669-2537
  - Submit the form via:
    - Fax to 1-888-613-7552

By completing the Prescriber Enrollment Form, the prescriber agrees to comply with the MYALEPT REMS Program requirements. A confirmation of your certification in the MYALEPT REMS program will be sent to you so you can begin to prescribe MYALEPT.

**Reporting Adverse Reactions**


Healthcare providers should report all suspected adverse events. Please contact the company at 1-855-669-2537 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch.com](http://www.fda.gov/medwatch.com).

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[Prescriber Enrollment Form](#)  
[PDF MYALEPT REMS Program Prescription Authorization Form](#)  
[PDF Prescribing Information](#)

**MYALEPT REMS Program Contact Us**  
**Phone:** 1-855-669-2537  
**Fax:** 1-888-613-7552  
**Hours of Operation:**  
Monday - Friday,  
8:00am-8:00pm  
Eastern Time



**11.3 mg per vial**

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MYALEPT™ REMS Program

**Program Requirements | Training & Enrollment**

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

AstraZeneca has worked with the FDA to develop the MYALEPT REMS Program:

To educate prescribers about

- the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the serious adverse events that may result from these antibodies,
- the risk of lymphoma, and
- appropriate patient selection

**REMS Materials**

- [PDF MYALEPT REMS Program: An Introduction](#)
- [PDF MYALEPT REMS Program Prescriber Training Module](#)
- [PDF MYALEPT REMS Program Prescriber Enrollment Form](#)
- [PDF MYALEPT REMS Program Prescription Authorization Form](#)
- [PDF Prescribing Information](#)

Program Requirements

MYALEPT is available only through the MYALEPT REMS Program. The MYALEPT REMS Program requirements include:

**For Prescribers:**

- **Certification** of prescribers of MYALEPT
  - Certification consists of completion of **training, and enrollment** in the MYALEPT REMS Program
- **Completion** of a Prescription Authorization form for **each** new prescription

Find out more about [Training & Enrollment](#).

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- **Restricted distribution** of MYALEPT to patients with completed Prescription Authorization Forms from prescribers who are certified in the MYALEPT REMS Program

Training & Enrollment

Healthcare providers who prescribe MYALEPT must review the prescriber training materials to enroll in the MYALEPT REMS Program.

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- 1. Review the Prescriber Education Materials**
  - [MYALEPT Prescribing Information](#)
  - [Prescriber Training Module](#)
- 2. Complete and submit the MYALEPT REMS Program Prescriber Enrollment Form**
  - Print and sign the [Prescriber Enrollment Form](#) or request a copy by calling 1-855-669-2537
  - Submit the form via:
    - Fax to 1-888-613-7552

By completing the Prescriber Enrollment Form, the prescriber agrees to comply with the MYALEPT REMS Program requirements. A confirmation of your certification in the MYALEPT REMS program will be sent to you so you can begin to prescribe MYALEPT.

Reporting Adverse Reactions

Healthcare providers should report all suspected adverse events. Please contact the company at **1-855-669-2537** or FDA at **1-800-FDA-1088** or [www.fda.gov/medwatch.com](http://www.fda.gov/medwatch.com).

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/s/  
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SUZANNE C BERKMAN ROBOTOM  
02/25/2014

CLAUDIA B MANZO  
02/25/2014

Concur with review. Entered a day after the action date due to technical errors that arose when attempting to enter it into DARRTS on 2/24/14.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 24, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Subject: Review of proposed REMS

- Revised REMS Document (Word)
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction*
- *Prescriber Training Module*
- Myalept REMS website
- REMS Supporting Document

Drug Name(s): Myalept (metreleptin)

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company (BMS) / AstraZeneca / Amylin

OSE RCM #: 2013-821

## 1 INTRODUCTION

This is a review of the proposed risk evaluation and mitigation strategy (REMS) for metreleptin BLA 125390 initially received March 27, 2013 and submitted revisions via email on February 20, 2014 and February 23, 2014.

This review is written by the Division of Risk Management (DRISK), in consultation with the Office of Prescription Drug Promotion (OPDP).

## 2 MATERIALS REVIEWED

- Proposed REMS. Submitted via email February 20, 2014
- OPDP REMS Consult Review; signed in DARRTS on February 20, 2014 by Jones K.

### Other DRISK reviews related to the March 27, 2013 submission

- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 19, 2014 by Robottom S and LaCivita C.
- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 14, 2014 by Robottom S and LaCivita C.
  - This review comments on and provides revisions to the REMS Document, Introductory Information Sheet titled *Myalept REMS Program: An Introduction*, REMS website, and REMS Assessment.
- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 5, 2014 by Robottom S and Manzo C.
  - This review provided comments on the REMS proposal and revisions to Prescriber Enrollment Form and Prescription Authorization Form
- Robottom S. DRISK REMS Options review for BLA 125390. Signed in DARRTS on November 26, 2013 by Robottom S and Manzo C.

## 3 COMMENTS TO THE REVIEW DIVISION

We reviewed the consult provided by OPDP. All but one of the comments were addressed through revisions to align the REMS materials with the most up-to-date version of the prescribing information. OPDP had compared earlier versions of the REMS materials to a different more recent version of the prescribing information.

OPDP provided the following comment on a statement that appears in several REMS materials:

“I agree to test for neutralizing activity in patients who experience severe infections or if I suspect MYALEPT is no longer working (i.e., **loss of glycemic control**, or increases in triglycerides.”

- OPDP is concerned that this statement minimizes the risks of the drug. The Warnings and Precautions section of the draft PI states, “Anti-

metreleptin antibodies with in vitro neutralizing activity to leptin associated with adverse events consistent with loss of endogenous leptin activity and/or loss of efficacy have been identified in two patients with generalized lipodystrophy treated with MYALEPT (severe infections, **increases in HbA1c** and triglycerides)....” (bolded emphasis added) In addition, the Adverse Reactions section of the draft PI states, “Adverse events reported in these two patients included severe infections and **worsening of metabolic control (increases in HbA1c and/or triglycerides).**” (bolded emphasis added) OPDP recommends revising this presentation in a manner consistent with the draft PI.

Minor fluctuations or worsening of a patient’s metabolic or glycemic status would not be cause to suspect neutralizing activity. Rather, persistent, marked worsening or “loss” of control would be more suggestive. Use of the phrase “loss of glycemic controls” was discussed with Dr. Golden, the primary medical officer. Dr. Golden agreed this phrase accurately explained the clinical status of a patient who should be tested for neutralizing activity. DRISK and DMEP agreed to maintain “loss of glycemic control” and did not accept OPDP’s recommendation.

#### **4 RECOMMENDATIONS FOR THE REVIEW DIVISION**

##### **Submission received via email on February 20, 2014**

Comments and revisions embedded in the appended documents were sent via email to BMS on February 21, 2014:

- Revised REMS Document (Word)
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction*
- Myalept REMS website

Comments and revisions to the REMS Supporting Document and *Prescriber Training Module* were sent to BMS on February 23, 2014.

##### **Submission received via email on February 23, 2014**

Comments and revisions embedded in the appended documents were sent via email to BMS on February 23, 2014:

- Revised REMS Document (Word)
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction* (note: not attached; no edits)
- *Prescriber Training Module*
- Myalept REMS website
- REMS Supporting Document (Word)

#### **ATTACHMENTS**

##### **Appendix 1: Comments on February 20, 2014 email submission**

- Revised REMS Document (Word)

- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction*
- *Prescriber Training Module*
- Myalept REMS website
- REMS Supporting Document (Word)

**Appendix 2: Comments on February 23, 2014 email submission**

- Revised REMS Document (Word)
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Prescriber Training Module*
- Myalept REMS website
- REMS Supporting Document (Word)

**Note:** The *Myalept REMS Program: An Introduction* is not attached. No edits were necessary.



## **Appendix 1: Comments on February 20, 2014 email submission**

- Revised REMS Document (Word)
- Prescriber Enrollment Form
- Prescription Authorization Form
- *Myalept REMS Program: An Introduction*
- *Prescriber Training Module*
- Myalept REMS website
- REMS Supporting Document (Word)

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SUZANNE C BERKMAN ROBOTOM  
02/24/2014

CYNTHIA L LACIVITA  
02/24/2014  
Concur

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

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

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**NDA/BLA #s:** 125390  
**Products:** Myalept (Metreleptin) Injection  
**SPONSOR:** Bristol-Myers Squibb Company  
**FROM:** Suchitra Balakrishnan, MD, PhD.  
**DATE:** January 23, 2014

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

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

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Myalept (metreleptin) to ensure that the benefits of the drug outweigh the serious risks associated with the development of neutralizing antibodies and risk of lymphoma. In reaching this determination, we considered the following:

- A. The prevalence of generalized lipodystrophy is unknown; however, a recent review<sup>1</sup> estimates 400 cases of generalized lipodystrophy have been reported worldwide (approximately 300 patients with congenital generalized lipodystrophy (CGL) and 100 patients with acquired generalized lipodystrophy (AGL)). Assuming that only one fourth of patients are reported, the prevalence of generalized lipodystrophy in the general population could be estimated at less than one in a million.

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<sup>1</sup> Garg A. Lipodystrophies: Genetic and acquired body fat disorders. J Clin Endocrinol Metab. 2011; 96(11): 3313-3325.

- B. Generalized lipodystrophy is characterized by the loss of body fat. As the hormone leptin is primarily produced by fat tissue, patients with generalized lipodystrophy are leptin-deficient. As a consequence of a lack of adequate storage depots for body fat (and resultant ectopic deposition of fat in tissues such as muscle and liver), as well as leptin-deficiency, patients with generalized lipodystrophy often have severe or life-threatening co-morbidities such as diabetes mellitus requiring hundreds of units of insulin daily or acute pancreatitis from extreme hypertriglyceridemia.
- C. In the pivotal BLA trial, patients with generalized lipodystrophy (congenital or acquired) with severe insulin resistance resulting in diabetes mellitus and / or severe hypertriglyceridemia not adequately controlled with other therapies appear to have achieved benefits from metreleptin that would be unlikely to have been achieved spontaneously. Mean (SE) hemoglobin (Hb)A1c change was -2.0 (0.3) % at month 12 from a baseline mean of 8.7 (0.4) %. The median change for triglycerides was -246.5 mg/dl at month 12 from a baseline median of 414.5 mg/dl. In addition, the improvements were accentuated in those patients with uncontrolled diabetes mellitus (defined here as HbA1c  $\geq$  7%; mean change from baseline in these patients was -2.4 (0.5) %) or severe hypertriglyceridemia (defined here as triglycerides  $\geq$  500 mg/dL; median change from baseline in these patients was -1117 mg/dl). Many of the patients studied who were on concomitant anti-hyperglycemic medications at baseline discontinued or had significant reduction in the doses of anti-hyperglycemics (including insulin) at Month 12.
- D. The expected duration of treatment is life-long.
- E. Despite the limited nature of the clinical trial database, two serious safety signals emerged.

Immunogenicity: Metreleptin is highly immunogenic. The majority of patients evaluated in the lipodystrophy trials developed anti-leptin antibodies (89%). At least five (7.7%) patients from the lipodystrophy trials have developed antibodies with neutralizing activity; however, the incompleteness of the current immunogenicity database precludes understanding of the magnitude and persistence of the observed anti-leptin antibody responses. At least one patient is known to have developed high-potency, highly reproducible, neutralizing anti-leptin antibodies associated with adverse events, a second patient's case is under review. The initial case is a 19 year-old female patient with CGL appeared to have loss of metabolic control in association with the neutralizing antibodies, and was additionally reported to have multiple hospitalizations for sepsis. Because of the role that leptin plays in the functioning of the immune system, it is theoretically possible that neutralizing antibodies to leptin could have implications for immune functioning (i.e., immunodeficiency), even in patients with very low endogenous leptin. A number of adverse events (excessive weight gain, glucose intolerance, diabetes mellitus) associated with the development of antibodies with neutralizing activity in patients treated with metreleptin in a

development program for the treatment of obesity has highlighted a potential risk for off-label use.

Additional unanswered questions related to the development of neutralizing antibodies in the lipodystrophy population are (1) whether a risk of maternal-fetal transfer of neutralizing antibodies exists and if so, what are the clinical consequences, and (2) what the potential immunogenicity risk would be to a nursing infant.

T-cell Lymphoma: Three cases of T-cell lymphoma have been reported in patients with AGL in the NIH trials. Two of the cases occurred in patients with hematological disease (neutropenia, lymphadenopathy) at baseline and who were on confounding medications, such as G-CSF and erythropoietin. A third patient (13-year-old with AGL) did not have any known hematological disorders or other confounding factors prior to developing lymphoma, aside from the AGL diagnosis (AGL is associated with autoimmune disease). Leptin is a cytokine that exerts its effect by binding to the leptin receptor on cell surfaces and activating the JAK-STAT intracellular pathway. Leptin signaling via JAK-STAT and other pathways promotes cell growth and survival and inhibits apoptosis. Dysregulation of STAT proteins and signaling contributes to the pathogenesis of some malignancies. Of note, hematological malignancies, including T-cell lymphoma, have been reported in the literature in patients with lipodystrophy not treated with metreleptin. It is unknown if metreleptin could promote the progression of lymphoma or other malignancies in a patient population that is predisposed to these diseases. The incidence of T-cell lymphoma in the general U.S. population for males is 2.3 per 100,000 and for females is 1.4 per 100,000<sup>2</sup>; by contrast, in the trials the incidence of T-cell lymphoma was 5.8% for males (a 2565-fold increase) and 1.9% for females (a 1357-fold increase). Because of the small population in the BLA clinical trials, these estimates have wide confidence intervals.

F. Myalept (metreleptin) is a new molecular entity.

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

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<sup>2</sup> Howlader N, et al. SEER Cancer Statistics Review, 1975-2009, National Cancer Institute. Bethesda, MD.

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/s/  
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SUCHITRA M BALAKRISHNAN  
02/24/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 19, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Subject: Review of Bristol-Myers Squibb's proposed REMS

- Revised *Prescriber Training Module*

Drug Name(s): Myalept (metreleptin)

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company

OSE RCM #: 2013-821

## **1 INTRODUCTION**

This is a review of Bristol-Myers Squibb (BMS) Company's proposed risk evaluation and mitigation strategy (REMS) for metreleptin BLA 125390 initially received March 27, 2013.

This review specifically provides comments and revisions to the *Prescriber Training Module* submitted in the original submission on March 27, 2013:

## **2 MATERIALS REVIEWED**

- BMS proposed REMS. Submitted March 27, 2013.

### **Other DRISK reviews related to the March 27, 2013 submission**

- Robottom S. DRISK REMS review for BLA 125390. Signed in DARRTS on February 14, 2014 by Robottom S and LaCivita C.
  - This review comments on and provides revisions to the REMS Document, Introductory Information Sheet titled *Myalept REMS Program: An Introduction*, REMS website, and REMS Assessment.
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- Robottom S. DRISK REMS Options review for BLA 125390. Signed in DARRTS on November 26, 2013 by Robottom S and Manzo C.

## **3 REVIEW FINDINGS**

The Prescriber Training Module was revised to be consistent with the Myalept Prescribing Information sent to BMS on Monday, February 17, 2014.

## **4 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Myalept REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the revised REMS Supporting Document as soon as possible.

The comments below are based on DRISK's preliminary review of the REMS proposal for Myalept; additional revisions may be necessary.

## **5 COMMENTS FOR THE APPLICANT**

You have now received comments on all the REMS materials (REMS document, prescriber enrollment form, prescription authorization form and assessment).

Revise the materials to reflect agreed upon labeling.



Once you have received comments on all the materials, we request that you re-submit the REMS materials via email to facilitate our timely review.

All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

### **1. PRESCRIBER TRAINING MODULE**

The Prescriber Training Module reflects the FDA version of the prescribing information sent to you on Monday, February 17, 2014. Please provide a mock-up pdf of the revised prescriber training module (along with the Introductory Information Sheet and Website, Prescriber Enrollment Form, and Prescription Authorization Form) and a Word version (track changes with your edits and clean).

Please submit the Word version as soon as possible (along with complete REMS). We understand the pdf may take additional time. The PDFs may be submitted later.

See attached revised Prescriber Training Module.

### **2. REMS SUPPORTING DOCUMENT**

The REMS Supporting Document must be consistent with all changes made to the REMS Document and Assessment Plan. Please revise accordingly and resubmit (Word version) for review.

### **3. GENERAL COMMENTS**

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

### **ATTACHMENTS**

- Prescriber Training Module

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/s/

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SUZANNE C BERKMAN ROBOTOM  
02/19/2014

CYNTHIA L LACIVITA  
02/19/2014  
Concur

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 14, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Kate Heinrich Oswell, M.A.  
Health Communications Analyst, DRISK

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Subject: Review of Bristol-Myers Squibb's proposed REMS

- Revised REMS Document
- Introductory Information Sheet
- Revised Website
- Revised REMS Assessment

Drug Name(s): Myalept (metreleptin)

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company

OSE RCM #: 2013-821

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## 1 INTRODUCTION

This is a review of Bristol-Myers Squibb (BMS) Company's proposed risk evaluation and mitigation strategy (REMS) for metreleptin BLA 125390 initially received March 27, 2013.

This review specifically provides comments and revisions to the following materials submitted in the original submission on March 27, 2013:

- REMS Document
- Introductory Information Sheet - *MYALEPT REMS Program: An Introduction*
- REMS Website
- REMS Assessment

## 2 MATERIALS REVIEWED

- BMS proposed REMS. Submitted March 27, 2013.

### Other DRISK reviews related to the March 27, 2013 submission

- Robottom S. DRISK REMS review for BLA 12390. Signed in DARRTS on February 5, 2014 by Robottom S and Manzo C.
  - This review provided comments on the REMS proposal and revisions to Prescriber Enrollment Form and Prescription Authorization Form
- Robottom S. DRISK REMS Options review for BLA 125390. Signed in DARRTS on November 26, 2013 by Robottom S and Manzo C.

## 3 REVIEW FINDINGS

The REMS document was reviewed by the Office of the Center Director (OCD) and the Office of Chief Counsel (OCC). The majority of the revisions to the document were made to align with CDER's current thinking. In addition, the following substantive revisions were made.

### Goals

DRISK proposed the following revised goal:

The goal of the MYALEPT REMS is to mitigate (1) the risks of serious adverse sequelae due to the development of anti<sup>(b) (4)</sup> antibodies <sup>(b) (4)</sup>  
<sup>(b) (4)</sup> (e.g., severe infections, excessive weight gain, glucose intolerance, diabetes mellitus) <sup>(b) (4)</sup> and (2) the risk of lymphoma by:

- Educating prescribers about the development of neutralizing antibodies, the serious adverse sequelae that may result from these antibodies, and the risk for lymphoma associated with MYALEPT

- Limiting the population exposed to MYALEPT by requiring prescriber attestation that each patient has a diagnosis consistent with the approved indication

Reviewer Comment:

(b) (6)

However, we do agree that prescriber certification re-enforces prescriber education about the risks and appropriate patient selection and pharmacy certification ensures that the Prescription Authorization Form is completed for each new prescription. Therefore, we aligned on the following revision.

*Limiting the population exposed to MYALEPT by requiring prescriber certification, pharmacy certification, and prescriber attestation that each patient has a diagnosis consistent with the approved indication*

#### **Dissemination of the Introductory Information Sheet**

DRISK proposed the following in under prescriber certification:

(b) (6)

(b) (6)

*Reviewer Comment: DRISK proposed that the introductory information sheet should be distributed through sales representatives at the time of first discussion of Myalept. OCD and OCC opined that the inclusion of a requirement to distribute materials through sales representatives could be problematic for abbreviated new drug applicants in the future and removed the language.*

#### **4 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Myalept REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the revised REMS Supporting Document as soon as possible.

The comments below are based on DRISK's preliminary review of the REMS proposal for Myalept; additional revisions may be necessary.

#### **5 COMMENTS FOR THE APPLICANT**

You have now received comments on all the REMS materials (REMS document, prescriber enrollment form, prescription authorization form and assessment) with the exception of the Prescriber Training Module. You will receive comments on this piece under separate cover.

Revise the materials to reflect agreed upon labeling.

Once you have received comments on all the materials, we request that you re-submit the REMS materials via email to facilitate our timely review.

All final REMS materials can be submitted via the gateway once they have been fully agreed upon by the Agency.

## **1. REMS DOCUMENT**

Please see the revised REMS Document.

Note that the revised REMS document is not in track changes.

While we have not materially changed the substance of the REMS program that you proposed, we have edited the text of the document to optimally describe the REMS program to be in line with CDER's current thinking.

## **2. MATERIALS**

- Please note that the Myalept-specific content of the revised materials is consistent with the FDA-revised labeling you received on February 3 and 4, 2014. Revise the materials accordingly based on agreed-upon labeling revisions.
- Regarding the mock-up pdf versions of your materials, we agree with the "Myalept brand" formatting with the exception of where we have noted a formatting change within the materials. For example, do not use "ALL CAPS" because it is more difficult to read. Please apply this as a global change throughout your materials.

### **A. Myalept REMS Program: An Introduction**

Remove the (b) (6) We recommend a single introductory information piece ( i.e., *MYALEPT REMS Program: An Introduction*) be distributed as part of the elements to assure safe use to communicate information about the risks and REMS program requirements.

Incorporate the "Myalept brand formatting" into this piece so the presentation is consistent across all the Myalept REMS materials.

Please see the *Myalept REMS Program: An Introduction*.

### **B. Website**

Please see the revised website.

## **3. REMS ASSESSMENT PLAN**

The following bullets outline the REMS Assessment Plan for Myalept.

**1. REMS Program Outreach**

(b) (4)

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**2. REMS Program Utilization Statistics**

(b) (4)

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(b) (4)

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C. Patient Utilization



(b) (4)

**3. Program Infrastructure and Performance**



(b) (4)

**4. Assessment of Prescribers and Pharmacists understanding of the following:**

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

#### **4. DEVELOPING SURVEY METHODOLOGY AND SURVEYS**

The following comments are to assist you in drafting your survey methodology and survey.

Submit for review the detailed plan you propose to use to evaluate patients', healthcare providers' understanding about the safe use of Myalept. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Myalept.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.

If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).

4. Ensure the sample is demographically representative of the population who use the drug (patients), prescribe the drug (doctors), or dispense the drug (pharmacists), regardless of the condition for which they use or prescribe it.
5. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
6. List the inclusion criteria for patients and healthcare providers. For example, eligible *patient* respondents must be:
  - Age 18 or older
  - Currently taking Myalept or have taken the drug in the past 3 months
  - Not currently participating in a clinical trial involving Myalept
  - Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

7. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

8. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
9. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to prescribe (doctors) or dispense (pharmacists) Myalept, and that their answers and personal information will be kept confidential and anonymous.

All text, including questions and answers, are to be non-promotional in language and tone.

10. Clarify in your methodology that respondents are eligible for one wave of the survey only.
11. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

You may stratify the data by any relevant variable, and also in aggregate. Submit with your assessments all methodology and instruments utilized.

12. Submit all methodology and instruments utilized with your assessments.

### **Healthcare Provider Survey**

13. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers' knowledge of the risks and safe use associated with Myalept.

The assessment does not assess healthcare providers' comprehension of the educational materials.

Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

14. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
15. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.

Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

16. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

17. Use the following (or similar) questions to assess receipt and use of the educational materials.
  - Prior to today, which of the following were you aware of or received with regard to Myalept? (Select all that apply)

<b>Educational Material</b>	<b>Aware</b>	<b>Received</b>
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
<i>Myalept REMS Program: An Introduction</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Myalept Training Module</i>	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

- Did you read the Full Prescribing Information?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
  - e) I did not receive the Myalept Full Prescribing Information
  
- Did you read the *Myalept REMS Program: An Introduction*?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
  - e) I did not receive the *Myalept REMS Program: An Introduction*
  
- Did you read the *Myalept Training Module*?
  - a) All,
  - b) Most,
  - c) Some,
  - d) None
  - e) I did not receive the *Myalept Training Module*
  
- Do you have any questions about any of the educational materials related to Myalept? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

## 5. REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS Document and Assessment Plan. Please revise accordingly and resubmit for review.

## 6. GENERAL COMMENTS

Resubmission Requirements and Instructions: Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

#### **ATTACHMENTS**

- Revised Myalept REMS Document
- *Myalept REMS Program: An Introduction*
- Revised REMS Website

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/s/  
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SUZANNE C BERKMAN ROBOTOM  
02/14/2014

CYNTHIA L LACIVITA  
02/14/2014  
concur

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: February 5, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Subject: Review of Bristol-Myers Squibb's proposed REMS

Drug Name(s): Metreleptin

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company

OSE RCM #: 2013-821



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## 1 INTRODUCTION

This is a review of Bristol-Myers Squibb (BMS) Company's proposed risk evaluation and mitigation strategy (REMS) for metreleptin BLA 125390 initially received March 27, 2013.

For an analysis of the benefits, risks, and risk management options for metreleptin, please refer to the DRISK review by Suzanne Robottom, signed in DARRTS on November 26, 2013.

### 1.1 BACKGROUND

Metreleptin is a recombinant analog of human leptin. It differs from human leptin by one additional amino acid. The proposed dosing is weight-based, once daily subcutaneous injection for self-administration. The BLA was submitted for review "for the treatment of metabolic disorder associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy."

On December 11, 2013 the Endocrinologic and Metabolic Drugs Advisory Committee voted 11 to 1 that the applicant "demonstrated substantial evidence that the benefits of metreleptin exceed the risks for the treatment of pediatric and adult patients with generalize lipodystrophy." The Committee voted 10 to 2 that the applicant did *not* "demonstrate substantial evidence that the benefits of metreleptin exceed the risks for the treatment of pediatric and adult patients with metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis."

Labeling negotiations are ongoing. The Division of Metabolism and Endocrinology Products (DMEP) recommends a Boxed Warning to address the risk of adverse events resulting from the development of anti-drug antibodies with neutralizing activity and lymphoma. DMEP recommends the following indication, limitations of use and contraindication:

Indication: MYALEPT (metreleptin for injection) is indicated as an adjunct to a reduced-calorie diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

#### Limitations of Use

- The safety and effectiveness of MYALEPT in the treatment of complications of partial lipodystrophy have not been established.
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including non-alcoholic steatohepatitis (NASH), have not been established.
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy.

- MYALEPT is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.

Contraindication: MYALEPT is contraindicated in patients with general obesity not associated with congenital leptin deficiency. MYALEPT has not been shown to be effective in treating general obesity, and the development of anti-leptin neutralizing antibodies have been reported in obese patients treated with MYALEPT.

## 2 MATERIALS REVIEWED

- Robottom S. DRISK REMS Options review for BLA 125390. Signed in DARRTS on November 26, 2013 by Robottom S and Manzo C.
- BMS proposed REMS. Submitted March 27, 2013.

## 3 SUMMARY OF APPLICANT'S PROPOSED REMS

BMS submitted a REMS with ETASU which includes prescriber certification, pharmacy certification, and documentation of safe use conditions through a Prescription Authorization Form. Each new prescription must be submitted using a required "Prescription Authorization Form" which requires the prescriber to attest that the patient has a diagnosis consistent with the approved indication for metreleptin.

This approach is consistent, in principle, with the REMS approved for Juxtapid (lomitapide; approved December 21, 2012) and Kynamro (mipomersen; approved January 29, 2013). Juxtapid and Kynamro are approved for use in an orphan population (homozygous familial hypercholesterolemia), a condition where, similar to metreleptin, a specific blood test or genetic test cannot be relied upon to make the diagnosis; rather, it is a clinical diagnosis. Also similar to metreleptin, the clinical development programs for Juxtapid and Kynamro were very small, and in the case of Juxtapid, were uncontrolled. The off-label population for Juxtapid and Kynamro include the much broader dyslipidemic population, similar to the broader off-label obesity population for metreleptin. All three of these programs had concerning safety signals despite small exposures – hepatotoxicity for Juxtapid and Kynamro, and lymphoma and immunogenicity for metreleptin.

The proposed REMS for metreleptin describes requirements for prescribers and pharmacies to certify in order to prescribe and dispense metreleptin, respectively

### 3.1 GOALS

BMS proposed the following goals for the Myalept REMS:

- To educate prescribers about:
  - the potential risk of lymphoma associated with the use of MYALEPT
  - the (b) (4) risk of (b) (4) the development of neutralizing activity to metreleptin; and

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

*Reviewer Comment: The goals of the REMS must be revised to include the overarching goal to mitigate the serious adverse events due to the development of neutralizing antibodies and with a risk of lymphoma followed by measureable objectives. This approach reflects DRISK's most current thinking and framework for writing goals based on the experience gained over the last several years of reviewing REMS and analyzing if the REMS is meeting its goals via the REMS assessments.*

*The prescribing information will not include [REDACTED] (b) (4)*

*The revised REMS document will be provided in a subsequent review.*

### **3.2 COMMUNICATION PLAN**

BMS did not propose a communication plan. [REDACTED] (b) (6)

*Reviewer Comment: In the DRISK Review signed November 26, 2013 we stated that a "multi-faceted approach to disseminate information to prescribers may increase the probability of informing [prescribers] about the risks..., appropriate use, and about REMS program requirements. This approach is consistent with Juxtapid and Kynamro."*

*Given that REMS seeks to limit the population exposed to metreleptin and it is not expected to be used broadly, we considered a more targeted communication approach was more prudent than [REDACTED] (b) (4). Therefore, DRISK recommends [REDACTED] (b) (4) create a short, introductory information sheet to communicate information about the risks and REMS program requirements. DRISK recommends the information sheet be distributed to healthcare providers either at the time of first discussion of metreleptin, or at the time a prescriber attempts to prescribe metreleptin and is not certified, or if a prescriber requests information about how to become certified.*

*The introductory information sheet supports the prescriber certification requirements and, as such, should be included as part of the corresponding element.*

### **3.3 ELEMENTS TO ASSURE SAFE USE**

The sponsor proposes the following elements:

- Prescriber certification: Prescribers must review the Prescribing Information and "Training Module" then complete the "Prescriber Enrollment form."

- Pharmacy certification: The sponsor plans to contract with a single specialty pharmacy distributor to distribute metreleptin.
- Documentation of safe use conditions: Prescribers attest on each “Prescription Authorization” form that:
  - ✓ I understand that Myalept is indicated.....[proposed indication].
  - ✓ I affirm that my patient has a clinical diagnosis consistent with inherited or acquired lipodystrophy, and that my patient (or caregiver) has been properly informed of the benefits and risks of Myalept therapy. I understand that Myalept is not indicated for use in patients with HIV-related lipodystrophy.
  - ✓ I understand that Myalept is not indicated for use in patients without concurrent evidence of inherited or acquired lipodystrophy.
  - ✓  (b) (4)

*Reviewer Comment: DMEP and DRISK discussed at length if prescriber attestation was a sufficient approach to limit use to the approved indication given concerns raised based on review of the first two Juxtapid REMS assessments which appear to indicate a different population is being prescribed Juxtapid in the post-marketing setting compared to the clinical trial population despite prescriber attestation. The team discussed the inclusion of one or more of the following parameters on the Prescription Authorization Form in attempt to assess or further characterize the population who is being prescribed metreleptin:*

- Leptin: There was general agreement that leptin was the most helpful laboratory value in assessing use of metreleptin but its utility may be limited because it is not part of the routine practice in the diagnosis of lipodystrophy. Therefore, very few values may be obtained.
- HbA1c and Triglycerides (TG): These laboratory parameters were analyzed as the primary efficacy endpoints for the BLA. These test results are more readily available (vs leptin) but would not be specific to lipodystrophy (could provide insight in disease severity but no information on what the underlying disease is (e.g., obesity)). Further, younger generalized lipodystrophy patients in the clinical trials tended to have less severe disease (lower HbA1c, lower TGs compared to adults with established disease). The population is anticipated to evolve in the post-marketing setting. Therefore, HbA1c and TG values may or may be difficult to interpret.
- BMI: BMI would identify obese patients but some lipodystrophy patients could have high BMI values.

*The team aligned that no additional parameters should be collected at this time. Based on the REMS assessments, these parameters may be revisited.*

### **3.4 IMPLEMENTATION SYSTEM**

BMS included an implementation system for the Myalept REMS Program to monitor and evaluate whether the elements to assure safe use are meeting the program’s goals.

*Reviewer Comment: The proposed implementation system is consistent with the approved REMS for Juxtapid and Kynamro but may require revisions to align with the Agency's current thinking regarding monitoring and evaluating whether the elements to assure safe use are meeting the program goals. This issue is under review with the Office of Regulatory Policy and Office of Chief Counsel.*

### **3.5 TIMETABLE FOR SUBMISSION OF ASSESSMENTS**

BMS proposed [REDACTED] (b) (4)

*Reviewer Comment: The proposed timetable is not consistent with the usual timetable for assessment for newly approved REMS with ETASU. The timetable will need to be revised so REMS assessments are received 6 months and 12 months from the date of initial REMS approval and then annually thereafter.*

## **4 RECOMMENDATIONS FOR THE REVIEW DIVISION**

The following comments on the Myalept REMS proposal should be sent to the applicant. Please advise the applicant to resubmit the REMS (e.g., REMS document and all REMS materials) and the REMS Supporting Document once they have received comments on all the pieces.

The comments below are based on DRISK's preliminary review of the REMS proposal for Myalept and additional revisions may be necessary. The REMS document is currently being cleared by the Agency, therefore comments on the REMS documents will be conveyed to the sponsor at later time. Appended to this review are some of the REMS materials with track changes.

## **5 COMMENTS FOR THE APPLICANT**

### **1. REMS DOCUMENT**

A REMS document with track changes will be provided under separate cover.

### **2. COMMUNICATION PLAN**

We agree that a Communication Plan is not needed.

### **3. ELEMENTS TO ASSURE SAFE USE**

- Clarify if prescribers will be able to enroll online through the metreleptin REMS website.

### **4. MATERIALS**

Please note that the Myalept-specific content of the revised materials is consistent with the FDA-revised labeling you received on February 3 and 4, 2014.

A. [REDACTED] (b) (6)

This piece will be provided under separate cover.

**B. Prescriber Enrollment Form**

Please see the revised Prescriber Enrollment Form.

**C. Prescription Authorization Form**

Please see the revised Prescription Authorization Form.

**D. Training Module**

Comment on the Training Module will be provided under separate cover.

**E. Website**

Comment on the website will be provided under separate cover.

**5. GENERAL COMMENTS**

Resubmission Requirements and Instructions: Once you have received comments on all the pieces submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

**6 REMS SUPPORTING DOCUMENT**

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

**ATTACHMENTS**

Prescriber Enrollment Form

Prescription Authorization Form

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUZANNE C BERKMAN ROBOTOM  
02/05/2014

CYNTHIA L LACIVITA  
02/06/2014  
concur



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: November 26, 2013

Reviewer(s): Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D.  
DRISK

Division Director: Claudia Manzo, Pharm.D.  
DRISK

Drug Name(s): Metreleptin

Therapeutic Class: recombinant leptin analog

Dosage and Route: weight-based subcutaneous injection for self-administration

Application Type/Number: BLA 125390

Applicant/sponsor: Bristol-Myers Squibb Company

OSE RCM #: 2013-821

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## **EXECUTIVE SUMMARY**

This review evaluates the need for a risk evaluation and mitigation strategy (REMS) for metreleptin and comments on the proposed REMS submitted by Bristol-Myers Squibb (BMS) on March 27, 2013.

The clinical data consists of two open-label, uncontrolled trials (n=100) in patients with lipodystrophy, and supporting safety information from the phase 2 studies conducted as part of the obesity clinical development program. Despite the limited nature of the clinical trial database, serious safety concerns emerged regarding the risks of lymphoma in lipodystrophy patients and immunogenicity, particularly in non-leptin deficient patients.

There have been three cases of T-cell lymphoma reported, all in patients with acquired generalized lipodystrophy, and one case of lymphocytic leukemia in a patient with obesity. The emergence of the serious sequelae (e.g., excessive weight gain, diabetes, sepsis) associated with the development of neutralizing antibodies is a concern particularly if metreleptin is used in a broader population in whom efficacy has not been determined.

To address these risks, BMS has proposed a REMS with elements to assure safe use (ETASU) consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions via a prescription authorization form. Based on the assessment of the risks and benefits, we agree that the proposed REMS constructs a restricted distribution system that would target use of metreleptin to the indicated population to the extent possible and work to ensure practitioners who do prescribe metreleptin are aware of the benefits and risks. We recommend that the risk management strategy be revised to include identifying patients by baseline leptin concentration, monitoring leptin concentrations, and/or monitoring antibody titers if ongoing analysis reveals utility in any of those parameters.

## **1 INTRODUCTION**

This review evaluates the need for a REMS for metreleptin and comments on the proposed REMS submitted by Bristol-Myers Squibb (BMS) on March 27, 2013.

Metreleptin is a recombinant analog of human leptin. It differs from human leptin by one additional amino acid. The proposed dosing is a weight-based, once daily subcutaneous injection for self-administration.<sup>1</sup>

Leptin is predominantly secreted by adipose tissue and plays a central role in neurohormonal regulation of energy homeostasis by inhibiting appetite. Leptin is also believed to play an important role in immunity and inflammation.

### **1.1 BACKGROUND**

The Metreleptin new drug application was submitted for review “for treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or

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<sup>1</sup> Golden J. Mid-cycle Meeting: Clinical Review. Presented September 26, 2013.

hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy” with the following proposed limitations of use:

- (1) Metreleptin is not indicated for use in patients with HIV-related lipodystrophy
- (2) Metreleptin is not for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy

The clinical data consists of two open-label uncontrolled trials (n=100) in patients with lipodystrophy, and supporting safety information from the phase 2 obesity clinical development program. Despite the limited nature of the clinical trial database, serious safety signals emerged that have prompted FDA to consider whether potentially serious risks can be mitigated.

## 1.2 REGULATORY HISTORY

The following table provides an overview of the metreleptin regulatory history:

Mar 1996	IND 50259 submitted by Amgen
Jun 2000	IND 60534 submitted by NIH to study metreleptin for lipodystrophy
May 2001	EOP2 meeting with Amgen <ul style="list-style-type: none"><li>• The Division agreed that study 991265 (8-month initial trial in 9 patients) was sufficient to use as the single pivotal trial in a leptin NDA</li><li>• The Division suggested that the NDA could be strengthened by following patients during a drug withdrawal and re-treatment period</li><li>• Concern about off-label use was raised; there was discussion about whether this could be addressed through restricted distribution</li></ul>
Aug 2001	Amgen was granted orphan designation for treatment of metabolic disorders secondary to lipodystrophy
Oct 2001	Amgen was granted fast track designation for the treatment of metabolic disorders associated with lipodystrophy
Mar 2006	Amylin assumed sponsorship of metreleptin from Amgen
May 2008	Treatment IND 101824 opened as a means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy
Feb 2009	FDA was notified of 2 cases of peripheral T cell lymphoma that occurred in the lipodystrophy program
May 2011	Meeting with Amylin to discuss 2 patients in the obesity program with neutralizing antibodies to metreleptin and excessive weight gain
Aug 2012	FDA was notified of a 3 <sup>rd</sup> patient in the obesity program with neutralizing antibodies to metreleptin and excessive weight gain
Jan 2013	FDA informed of 3 <sup>rd</sup> patient in the lipodystrophy program diagnosed with lymphoma
Aug 2013	FDA was notified of 1 <sup>st</sup> patient in the lipodystrophy program with category E (high potency, reproducible) neutralizing antibodies to metreleptin – hospitalized twice for sepsis

## 2 MATERIALS REVIEWED

The following materials were reviewed:

- BMS proposed REMS. Submitted March 27, 2013.
- BMS Advisory Committee Briefing Document.
- FDA Advisory Committee Briefing Document.

## 3 RISK BENEFIT CHARACTERIZATION

### 3.1 LIPODYSTROPHY AND TREATMENT OPTIONS<sup>1,2,3</sup>

Lipodystrophy is a clinically heterogeneous group of very rare disorders (~1350 cases reported in the literature). Lipodystrophy is categorized as inherited or acquired. Certain acquired lipodystrophy syndromes are thought to be autoimmune in nature.

Lipodystrophy is further characterized by the extent of deficiency or destruction of adipose cells resulting in a generalized, partial, or localized loss of adipose tissue. The extent of fat loss determines the severity of metabolic and other complications. The profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream (with resultant hypertriglyceridemia) and ectopic deposition of fat in non-adipose tissues (such as liver and muscle) and metabolic abnormalities including insulin resistance and diabetes. Lipodystrophy is often associated with severe metabolic abnormalities that can result in life-threatening co-morbidities such as acute pancreatitis from extreme hypertriglyceridemia, cirrhosis resulting from long-standing steatohepatitis, and/or accelerated atherosclerosis.

Because leptin is made in adipose tissue, lipodystrophy patients are relatively leptin-deficient. The relative leptin deficiency observed in this disease contributes to hyperphagia, which exacerbates the metabolic abnormalities as patients ingest more fat than they are able to dispose.

By treating leptin deficiency, it is hypothesized that metreleptin improves several of these metabolic abnormalities including diabetes and hypertriglyceridemia. The goal of metreleptin treatment is to lessen the metabolic complications of lipodystrophy; metreleptin does not treat the underlying pathology.

There are no treatments specifically approved to treat lipodystrophy.<sup>4</sup> Treatment is focused on managing the metabolic complications through diet modification and pharmacologic intervention with anti-hyperglycemic agents and/or lipid-lowering agents.

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<sup>2</sup> Garg A. Lipodystrophies: Genetic and acquired body fat disorders. *J Clin Endocrinol Metab.* 2011;96(11):3313-3325.

<sup>3</sup> Garg A. Acquired and inherited lipodystrophies. *N Engl J Med.* 2004;350(12):1220-34.

<sup>4</sup> There is one approved treatment for a *complication* of lipodystrophy. Egrifta (tesamorelin), a growth hormone releasing factor analog approved in 2010 for “the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.” Tesamorelin does not improve the metabolic complications associated with lipodystrophy. In fact, “glucose intolerance” is listed in the Warnings and Precautions section. Therefore, comparing benefits and risks is not informative.

More than likely, metreleptin would be used in combination with these other adjunctive treatments as was the case in the trials submitted to support approval.

Patients with more severe abnormalities often do not adequately respond to anti-hyperglycemic agents and/or lipid-lowering agents. In addition, the hyperphagia associated with lipodystrophy makes adherence to strict dietary therapy very difficult.

There is an unmet medical need for treatment in this patient population.

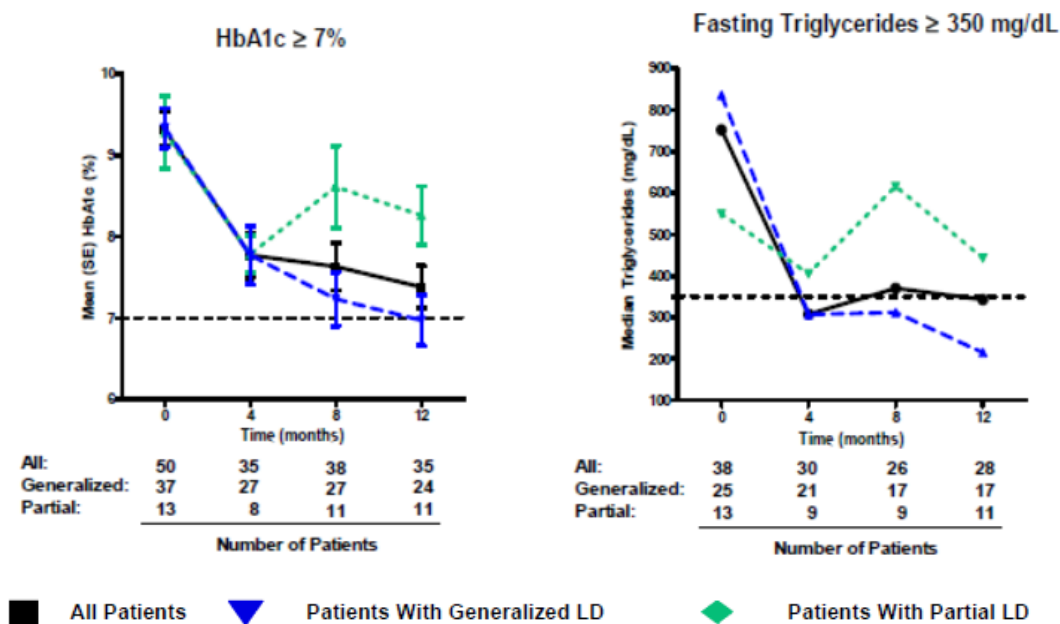
### 3.2 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Lipodystrophy is an orphan disease. The efficacy data is summarized below. A comprehensive review of these data can be found in the clinical review by Dr. Julie Golden.

The primary efficacy dataset for this BLA consists of 72 patients who have been treated with metreleptin in an open-label trial through NIH. An additional 28 patients with lipodystrophy have been treated with metreleptin under a treatment protocol to provide expanded access; data from these patients are considered supportive. Most patients were female with age ranging from 1 to 68 years.

Because metreleptin impacts the complications of the disease, the primary efficacy endpoints are improvements in hemoglobin (Hb) A1c, fasting plasma glucose (FPG), and fasting triglycerides (TG).

Baseline values in the pivotal NIH trial were: mean HbA1c 8.0%, mean FPG 176.7 mg/dL, and median fasting TG 359.0 mg/dL.<sup>5</sup> The figure below illustrates the change in HbA1c and TGs at month 12 for all patients and stratified by general and partial lipodystrophy patients.



<sup>5</sup> Efficacy data provided by DMEP and presented to CDER senior management on October 24, 2013.

- *Overall*, at Month 12, there was a mean decrease in HbA1c (-1.4%, 95% CI -1.8, -0.9); mean decrease in FPG (-41.8 mg/dL, 95% CI: -65.2, -18.4), and median decrease in TG (-44.8%).

However, the response to treatment was highly variable, confounded by the use of concomitant medications, and in some cases, difficult to assess due to the nature of the disease (heterogeneous, without a well-defined natural history), lack of placebo control, missing data, alternative baselines, and inadequately captured medication and dietary compliance.

- Nevertheless, the available data suggest a robust HbA1c response in patients with *generalized* lipodystrophy and uncontrolled diabetes mellitus (baseline HbA1c 7% or greater): Year 1 mean (SD) HbA1c change -2.4% (1.52); (baseline FPG 126 mg/dL or greater): Year 1 mean (SD) FPG change -82.1 mg/dL (75.45). In addition, patients with generalized lipodystrophy with baseline TG 500 mg/dL or greater had a median change from baseline in TG of -82.1% at Year 1. Some of these patients were able to decrease or discontinue concomitant anti-hyperglycemic medications, including some patients who were on high doses of insulin at baseline.

These results are in contrast to those in patients with partial lipodystrophy, who had considerably more variable and confounded responses, or in lipodystrophy patients without baseline metabolic abnormalities who generally did not experience clinically significant changes in the key efficacy parameters.

Patients have been treated for up to 11 years with metreleptin (exposure > 9 years, n=7; median length of treatment in NIH trial was 2.7 years [2mos – 11yrs; 83% of patients treated > 1yr]).

### 3.3 SAFETY CONCERNS

During the BLA review, two risks emerged as the primary safety concerns (summarized below). A comprehensive review of these safety issues can be found in the clinical review.

#### 3.3.1 Lymphoma

There have been three cases of T-cell lymphoma reported, all in patients with acquired generalized lipodystrophy, and one case of lymphocytic leukemia in a patient with obesity.

The Division of Hematology Products (DHP) was consulted to review the events of T-cell lymphoma that occurred in patients with lipodystrophy.<sup>6</sup> The correlation between metreleptin and the development of lymphoma in the first two lipodystrophy patients was confounded by symptoms of myelosuppression, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy. In addition, the second patient was taking erythropoietin, and had lymphadenopathy,

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<sup>6</sup> McGinn K. Memorandum – Consult Response. Division of Hematology Products. Signed by McGinn K, De Claro R, and Kaminskis E on March 5, 2013 under IND 101824.

hepatosplenomegaly, and skin lesions before starting metreleptin. Information about the third lipodystrophy patient is incomplete; however, she did not have any known hematological disorders at baseline.

The incidence of T-cell lymphoma in the general U.S. population is 2.3 per 100,000 men and 1.4 per 100,000 women. There is no information in the literature regarding the specific risk of lymphoma in non-HIV lipodystrophy patients. In the trials the incidence of T-cell lymphoma was 5800 per 100,000 males (a 2565-fold increase) and 1900 per 100,000 females (a 1357-fold increase). DHP could not determine whether the increased risk of lymphoma was related to the underlying condition or the treatment.

The DHP consult states that it is biologically plausible that metreleptin impacts susceptibility to non-Hodgkin lymphoma (NHL) and other malignancies. It is a cytokine that uses the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway for signal induction. Leptin binding activates JAKs, which in turn phosphorylates cytokine receptors which allows selective binding of the STAT family. Dysregulation of STAT proteins contributes to the pathogenesis of various types of lymphoid malignancies. Leptin exerts proliferative and antiapoptotic activities in a variety of cell types, including T-lymphocytes, leukemia cells, and hematopoietic progenitors. In vivo, leptin regulates inflammation, playing an inhibitory role on monocyte/macrophage-mediated responses while exerting a permissive role on lymphocyte-mediated inflammation.

Appendix A includes a list of other cancers reported in the lipodystrophy and obesity clinical trials.

### 3.3.2 Immunogenicity

The Office of Biotechnology Products describes metreleptin as a product at “high risk for anti-drug antibody generation with potential immunodeficiency syndrome” due to their assessment of patient and product-related factors.

The Division of Pulmonary Allergy and Rheumatology Products (DPARP) agrees that metreleptin is highly immunogenic. The majority of patients exposed in clinical trials develop anti-leptin antibodies. The clinical relevance with regard to safety is difficult to determine because the clinical trials did not include a comparator, not all patients had antibody titers drawn and titers were not drawn in a systematic fashion, complications of antibody-induced leptin deficiency mimic lipodystrophy, and the natural history of lipodystrophy is diverse and not well-characterized. The following describe adverse events reported in patients with documented neutralizing antibodies:

- Lipodystrophy patients: A 19 year old female with congenital generalized lipodystrophy received metreleptin treatment for three years. She developed neutralizing antibodies (category C<sup>7</sup>) in year 2 associated with loss of efficacy (increase in HbA1c). Between (b) (6) she was hospitalized five times for infection (Gemella species (b) (6)), Streptococcus viridans ( (b) (6) and (b) (6)), stenotrophomonas maltophilia (b) (6), acinetobacter baumannii

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<sup>7</sup> The sponsor developed categories to describe the neutralizing activity; A through E. “Category E” represents “high-potency, highly reproducible” neutralizing anti-leptin antibodies.



(b) (6). She developed neutralizing activity category E sometime between her year 2 and year 3 blood work. There is concern that antibody-induced leptin deficiency further compromised her immune system; increasing her susceptibility to infection.

Two additional lipodystrophy patients from the NIH trial and 3 patients from the treatment IND who developed neutralizing antibodies (all category C) have been reported.

- NIH Trial: One patient was considered a non-responder, but compliance was suspected to be an issue. She was continued on therapy and reportedly had improvement in HbA1c and the most recent antibody assessment was no longer determined to be neutralizing. The second patient had stable metabolic parameters, however she developed T-cell lymphoma (anaplastic large cell lymphoma) at Year 2.
- Treatment IND: None of the 3 patients from the treatment IND with neutralizing antibodies were reported to have significant metabolic sequelae (although none had HbA1c > 6% at baseline) or adverse events, and all 3 patients reverted from antibodies with neutralizing activity to without (1 of the 3 patients reverted back to positive neutralizing activity on the last available test).
- Obese patients: The sponsor was investigating the use of metreleptin as monotherapy and in combination with pramlintide (a human amylin analog) for the treatment of obesity. In 579 patients exposed to metreleptin in the metreleptin/pramlintide trials, three patients have been identified with Category D or E neutralizing activity. In March 2011 Amylin voluntarily discontinued the obesity development program (IND 50259, 110487) after the first two patients developed neutralizing antibodies associated with excessive weight gain, development of glucose intolerance or diabetes, and decreased leptin concentrations. In these three patients, neutralizing activity continued to be detected for at least 8 months to 4.5 years after metreleptin was discontinued. One of these three patients developed detectable neutralizing activity only after discontinuing treatment.

Obesity is considered a leptin-resistant or leptin-intolerant state. With the development of neutralizing antibodies, obese patients transition from resistant/intolerant to leptin-deficient. This can induce hyperphagia and excessive weight gain. Other potential complications could include metabolic sequelae of severe obesity, such as insulin resistance/diabetes mellitus, and effects on the immune system (i.e., immunodeficiency).

It is not known if neutralizing antibodies will eventually develop in all patients, if there are certain patients at higher risk, what the effect(s) will be, or whether the effect(s) will persist. It is also not known what effects maternal transfer of anti-leptin antibodies may have on a developing fetus.

There is no known treatment for neutralizing antibodies other than to discontinue the medication. The duration, persistence and reversibility of the effects is not known. Of the

obese patients who developed neutralizing antibodies: (1) stabilized weight (64 kg above baseline weight) 4.5 years after study discontinuation, (2) by self-report, lost the excess weight that had been gained (13 kg from study baseline), and (3) gained 26 kg over 8 months after study discontinuation but then was lost to follow-up.

### 3.3.3 Potential for Broader use

Metreleptin has been studied<sup>8</sup> for use in treating obesity (monotherapy and in combination with pramlintide), obesity in patients with type 2 diabetes mellitus, hypothalamic amenorrhea, hypoleptinemic HIV-infected patients with lipodystrophy, type 1 diabetes, nonalcoholic steatohepatitis with relative leptin deficiency, and other conditions.

The review team's primary concern is the potential for metreleptin's off-label use as a weight loss product. Metreleptin had a minimal weight loss effect when evaluated as monotherapy, but preliminary data suggested some additional weight loss benefit as an add-on to pramlintide in a subsequently halted obesity development program.

Even if the incidence of neutralizing antibody development is very low, use in a broader population such as the obesity population could result in a substantial number of people developing a worse metabolic state than before metreleptin treatment. It is not yet clear if discontinuing metreleptin treatment will return a patient to baseline.

Metreleptin has not been adequately studied in these populations to make a determination on the safety or efficacy for these or other non-lipodystrophy, non-leptin deficient indications. Therefore, given the potential severity of these risks and lack of data, there is concern that any potential benefit from metreleptin use in these broader populations will be outweighed by these risks.

## 4 RISK MANAGEMENT CONSIDERATIONS

The following three bullets provide an overview of drugs with approved REMS to address cancer, immunogenicity, and targeted use:

- **Cancer/Lymphoma:** Cancers/lymphoma are addressed in REMS with CPs for Actemra, Bydureon, Forteo, Gattex, Stelara, Victoza, and Nplate (modified REMS approved 12/2011) and with REMS with ETASU (ESAs, Nplate/Promacta (initial approval). For the drugs approved with REMS-CP, the cancer risk was initially classified as a theoretical risk in each case.<sup>9</sup>

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<sup>8</sup> Uses listed represent studies completed regardless of positive or negative efficacy findings.

<sup>9</sup> **Forteo, Bydureon, Victoza** – the cancer risk is theoretical because it is based on animal data, the clinical relevance is unknown. **Actemra** – this REMS includes a laundry list of risks – demyelinating disorders and malignancy are qualified as “potential risks” the rest of the risks do not have that qualifier. Malignancy was observed in the clinical trials but the risk is described it as “an immunosuppressant and treatment with immunosuppressants may result in an increased risk of malignancy.” **Stelara** - the initial risk was for cancer was pharmacologic/animal-based. In 1/2013 – the PI was revised to include PM reports of the rapid appearance of multiple cutaneous squamous cell carcinoma in pts with pre-existing risk factors for developing non-melanoma skin cancer. The REMS was updated in 9/2013. **Gattex** – label states “based on pharmacologic activity and findings in animals...” **Nplate** – there were a few human cases in the clinical trials but there was not consensus about its association with Nplate. The signal over time has become more concerning.

- Immunogenicity: The initial REMS-ETASU approved for Nplate included immunogenicity among a number of other risks. There are no currently approved REMS that address this risk in the goals.
- Targeted use: There are four REMS-ETASU (prescriber and pharmacy certification) that specifically mention limiting use in the goals including Avandia,<sup>10</sup> Juxtapid, Kynamro, and transmucosal immediate-release fentanyl products. In addition, Omontys is approved with a REMS-CP.<sup>11</sup> While the goals of the Tysabri REMS do not include restricting use to the labeled indications, the REMS materials preclude use for diseases that are not the approved indications.

The following are two specific considerations with metreleptin:

- There is not a single or specific series of laboratory tests that could be relied upon to confirm a diagnosis of lipodystrophy that could be required as a safe use condition of the REMS. Diagnosis of lipodystrophy relies on clinical judgment taking into account a variety of laboratory and physical exam findings along with the patient's family and medical history. It is a heterogeneous disease resulting in a diverse presentation and disease course; bearing some resemblance to other, more common metabolic disorders.<sup>12</sup>
- The utility of identifying patients by baseline leptin concentration, monitoring leptin concentrations, and/or antibody titers as possible risk mitigation strategies are subject to ongoing analysis and discussion. Therefore, the risk management strategy presented below does not include these as components/requirements at this time.

The following strategy would provide a mechanism to support prescribers in the safe use of metreleptin in the targeted lipodystrophy population, while deterring its use in a larger population of patients in whom neutralizing antibody development could lead to serious metabolic and immunologic complications.

The REMS proposed by the sponsor is consistent with regard to the goals and elements to assure safe use for the REMS approved for Juxtapid (lomitapide) and Kynamro (mipomersen).<sup>13</sup> Juxtapid and Kynamro are approved for use in an orphan population (homozygous familial hypercholesterolemia), a condition where, similar to metreleptin, a specific blood test or genetic test cannot be relied upon to make the diagnosis; rather, it is a clinical diagnosis. Also similar to metreleptin, the clinical development programs for Juxtapid and Kynamro were very small, and in the case of Juxtapid, were uncontrolled. The potential use of Juxtapid and Kynamro include the much broader dyslipidemic

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<sup>10</sup> The Avandia REMS was revised on November 25, 2013 removing the prescribing and dispensing restricted distribution requirements. <http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm>.

<sup>11</sup> The Omontys CP address risk in a broader populations through education about the approved indication. The REMS includes a DHCP letter distributed at approval and 1 year after approval. There is a specific link to the DHCP letter on the website for 2 years. In addition, the sponsor is only distributing to dialysis centers. This was a voluntary commitment and not required through the REMS.

<sup>12</sup> AACE Consensus Statement: The clinical approach to the detection of lipodystrophy. *Endocrine Prac.* 2013;19(1):107-116.

<sup>13</sup> Juxtapid was approved on December 21, 2012. Kynamro was approved on January 29, 2013.

population, similar to the broader obesity population for metreleptin. All three of these programs had concerning safety signals despite small exposures – hepatotoxicity for Juxtapid and Kynamro, and lymphoma and immunogenicity for metreleptin.

## 5 APPLICANT’S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

### 5.1.1 Goals

The proposed goals of the MYALEPT REMS are:

1. To educate prescribers about:
  - the potential risk of lymphoma associated with the use of MYALEPT
  - the (b) (4) development of neutralizing activity to metreleptin;
  - (b) (4)
2. To restrict access to therapy with MYALEPT to pediatric and adult patients with inherited or acquired lipodystrophy.

*Reviewer Comment: The review team agrees that lymphoma and immunogenicity should be the focus of the REMS. However, (b) (4) ” is not the primary concern with the development of neutralizing antibodies. It is not clear what, if any, monitoring could mitigate the risks and discussion is on-going regarding the utility of monitoring leptin concentration or antibody titer. Therefore, the goals will be revised based on the on-going discussion with the review team and further informed by the Advisory Committee.*

### 5.1.2 Medication Guide

The sponsor proposes a Medication Guide as part of labeling, not part of the REMS.

*Reviewer Comment: We agree with this approach because the REMS is focused on educating the prescriber regarding the appropriate use and risks associated with metreleptin. Appropriate prescribing is the primary risk management strategy which relies on the prescriber. While patient understanding is always important, it is not a necessary element for the success of the REMS.*

*This is consistent with the approved REMS for Kynamro and Juxtapid.*

### 5.1.3 Communication Plan


The sponsor does not propose a communication plan. (b) (6)

*Reviewer Comment: A multi-faceted approach to disseminate information to prescribers may increase the probability of informing them about the risks associated to these products, appropriate use, and about REMS program requirements.*

*This is consistent with the approved REMS for Kynamro and Juxtapid.*

#### 5.1.4 Elements to Assure Safe Use

The sponsor proposes the following elements:

- **Prescriber certification:** Prescribers must review the Prescribing Information and “Training Module” then complete the “Prescriber Enrollment form.”
- **Pharmacy certification:** The sponsor plans to contract with a single specialty pharmacy distributor to distribute metreleptin.
- **Documentation of safe use conditions:** Prescribers attest on each “Prescription Authorization” form that:
  - ✓ *I understand that Myalept is indicated.....[proposed indication].*
  - ✓ *I affirm that my patient has a clinical diagnosis consistent with inherited or acquired lipodystrophy, and that my patient (or caregiver) has been properly informed of the benefits and risks of Myalept therapy.*
  - ✓ *I understand that Myalept is not indicated for use in patients with HIV-related lipodystrophy.*
  - ✓ *I understand that Myalept is not indicated for use in patients without concurrent evidence of inherited or acquired lipodystrophy.*
  - ✓  (b) (4)

*Reviewer Comment: The proposed ETASU and prescription authorization form attestations are consistent with the approved REMS for Kynamro and Juxtapid.*

*For HCPs to become certified, they would be required to read educational materials and enroll in the metreleptin REMS program by acknowledging an understanding of the risks associated with metreleptin therapy and the approved indication for use. They would also agree to counsel patients about the risks identified in the REMS.*

*In addition, the certified prescriber will need to attest as part of writing the prescription via a “prescription authorization” form, that he/she is aware of the indication for metreleptin and the drug is medically appropriate for the patient. The prescription authorization form, would be completed and signed by the prescriber and sent to the certified pharmacy. The form would not require a patient signature.*

*The pharmacy certification tool serves to enforce prescriber certification and the safe use condition to ensure that only those prescribers who have been fully apprised of the benefits and risks are prescribing metreleptin and affirm the lipodystrophy diagnosis with each prescription (i.e., by using the required Prescription Authorization Form). To become certified to dispense metreleptin, a pharmacy must have procedures in place to verify that metreleptin is prescribed by a certified prescriber and the prescriber completes the prescription authorization form for each metreleptin prescription.*

### 5.1.5 Implementation System

The sponsor proposes a system to ensure that prescribers and pharmacies are certified before a patient receives metreleptin. This includes appropriate elements to facilitate implementation of the program (e.g., Call Center, materials available through various mechanisms), program monitoring (e.g., auditing) and evaluation.

### 5.1.6 Timetable for Submission of Assessments

The sponsor has proposed [REDACTED] (b) (4).

*Reviewer Comment: The timetable will need to be revised to be consistent with the standard timetable for REMS with ETASU (6 months, 12 months, and then annually thereafter).*

### 5.1.7 Information Needed for Assessment

The sponsor proposes the following:

- [REDACTED] (b) (6)

[REDACTED] (b) (4)

*Reviewer Comment: The proposed assessment includes a number of the metrics typically included in a REMS with prescriber and pharmacy certification. We note the proposal does not include*

*A successful REMS for metreleptin would (1) ensure appropriate patient selection for treatment with metreleptin and (2) educate prescribers about appropriate patient selection as described in the indication, the risks of lymphoma and possible sequelae related to the development of immunogenicity.*

*The success of the REMS could be measured by assessing:*

- The number/percentage of prescriptions successfully dispensed for metreleptin by practitioners who are certified.*
- The number/percentage of prescriptions successfully dispensed for metreleptin by pharmacies that are certified.*
- The number of patients receiving metreleptin would be similar to the size of the indicated patient population.*
- Treatment delays resulting from the REMS requirements*
- Prescriber understanding of the indication and risks*

#### **5.1.8 Other Risk Management Activities Proposed by the Sponsor**

In addition to the MG and REMS described above, BMS proposes:

- [Redacted]

## 6 ASSESSMENT OF NEED FOR A REMS

The scope and magnitude of adverse events related to neutralizing antibodies are not well-characterized. Based on the limited data currently available, the emergence of the serious sequelae (e.g., excessive weight gain, diabetes, sepsis) potentially associated with the development of neutralizing antibodies is a concern particularly if metreleptin is used in a broader population in whom efficacy has not been determined.

The primary concern is the potential for metreleptin's use as in a broader population of patients who are not leptin-deficient. Even if the incidence of neutralizing anti-leptin antibody development is very low, use in a broader population such as the obesity population could result in a substantial number of people developing a worse metabolic state than before metreleptin treatment. Given that in 2009-2010, 35.7% of U.S. adults were obese<sup>14</sup> and the resulting public interest in weight loss therapies, without any restrictions, use of metreleptin as a weight loss product could quickly exceed its intended use, although we acknowledge this may be impacted by the drug's cost and/or insurance coverage requirements.

In addition, it is difficult to predict who the likely prescribing population for metreleptin. Because of the rarity of lipodystrophy, very few physicians, including endocrinologists, have experience treating lipodystrophy patients. Many practitioners have experience treating the associated metabolic abnormalities. Likely, such patients would be referred to a specialist experienced in the diagnosis and management of the disease. It is also possible that patients would be diagnosed by a specialist and receive ongoing care from their primary care physician. If healthcare providers (HCP) prescribe metreleptin for conditions other than lipodystrophy (i.e., obesity/weight loss, HIV-lipodystrophy), there is concern that non-lipodystrophy HCPs may not be as well-versed in recognizing the signs/symptoms of leptin-deficiency induced by neutralizing antibodies.

Based on the assessment of these issues described above, the combination of prescriber certification, pharmacy certification, and documentation of safe use conditions through a "prescription authorization form" constructs a restricted distribution system that would target use of metreleptin to the indicated population to the extent possible and work to ensure practitioners who do prescribe metreleptin are aware of the benefits and risks.

- Prescribing metreleptin will be contingent on the prescriber being certified – attesting to understanding the risks and agreeing to the REMS requirements.
- Dispensing metreleptin will be contingent on the prescriber being certified AND attesting to the medical appropriateness of each metreleptin prescription.

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<sup>14</sup> Adult obesity facts. <http://www.cdc.gov/obesity/data/adult.html>. Accessed November 21, 2013.



Lipodystrophy is a heterogeneous disease that requires clinical judgment for diagnosis. There is not a single or specific series of laboratory tests that confirm diagnosis to leverage as a safe use condition. Therefore, in order to restrict use to the indicated population and not unduly constrain use, the most rationale approach is to rely on prescriber attestation.

At this time, we do not propose including patient enrollment as a component of the REMS, or specific patient monitoring linked to dispensing. The utility of identifying patients by baseline leptin concentration, monitoring leptin concentrations, and/or antibody titers as possible risk mitigation strategies are subject to ongoing analysis and discussion. A requirement to enroll patients in the REMS program does not contribute to achievement of the REMS unless there is adequate evidence to suggest baseline evaluation or periodic monitoring will contribute to the safe use of metreleptin. If approved, the availability of new data or additional safety information would be considered with respect to potential implications on REMS requirements.

## 7 CONCLUSION

The following were considered when assessing the risk benefit profile for metreleptin and possible risk management strategies commensurate with this profile.

- Lipodystrophy is a serious disease with complications that are difficult to manage with the currently available treatment options.
- Patients with generalized forms of lipodystrophy and significant insulin resistance appear to achieve the most benefit from metreleptin treatment, including large and, in some cases, sustained improvements in HbA1c and TG, often accompanied by a discontinuation or decrease of anti-hyperglycemic or lipid-lowering therapies.

Whether or not there is a subset of partial lipodystrophy patients with very low leptin concentrations and significant metabolic disease that also derive benefit is under discussion.

- Serious sequelae associated with the development of neutralizing antibodies particularly in non-leptin-deficient patients could result in a worse metabolic state than prior to metreleptin treatment.
- Metreleptin has not been adequately studied in broader populations to make a determination on the safety or efficacy for other indications. Therefore, given the severity of these potential risks and lack of data, any potential benefit in these broader populations is outweighed by these risks.
- The risk can be minimized by targeting use to the appropriate patient population.

Further the apparent signal of increased incidence of lymphoma in lipodystrophy patients is concerning and we acknowledge it is difficult to minimize beyond communicating the risk and targeting use to the appropriate patient population to maximize benefit.

We agree with the REMS approach proposed by the sponsor. We believe it would support appropriate use of metreleptin to the extent possible given the complexities of the diagnosis, allowing it to be available for use by informed prescribers for a targeted patient population to treat a life threatening illness with limited therapeutic options, while

protecting the broader patient populations. The risk management strategy should be revised if additional analysis reveals utility in identifying patients by leptin concentration, monitoring leptin concentrations, and/or monitoring antibody titers.

On October 24, 2013, DRISK and DMEP presented this recommendation to senior level management from Office of New Drugs, Office of Surveillance and Epidemiology, and Office of Regulatory Policy, Office of the Center Director, Office of Chief Counsel. There was general consensus that a REMS with ETASU is appropriate to ensure that the benefits outweigh metreleptin's risks and the final decision would be further informed by the Advisory Committee on December 11, 2013.

## ATTACHMENTS

### Appendix A: Cancer in Metreleptin Trials

- Hematological malignancies:
  - ML: 3 cases of T-cell lymphoma, all in patients with AGL, and 1 case of lymphocytic leukemia in a patient with obesity
  - Pbo: none reported
- Papillary thyroid cancer:
  - ML: 1 case in patient with CGL, and 2 cases in patients with obesity
  - Pbo: none reported
- Breast cancer:
  - ML: 1 case in a patient with FPL, 1 case in a patient with AGL (T-cell lymphoma patient), and 2 cases in patients with obesity
  - Pbo: 1 case in a patient with obesity
- Skin cancer:
  - ML: 2 cases of malignant melanoma and 2 cases of basal cell carcinoma, all in patients with obesity; 1 case of squamous cell carcinoma of the tongue in a patient with HIV-related lipodystrophy
  - Pbo: 2 cases basal cell carcinoma in patients with obesity
- Others :
  - ML: 1 case of metastatic adenocarcinoma (AGL) and 1 case of bile duct cancer (lipodystrophy patient in Japan); also 1 case of vaginal carcinoma in a patient treated with Fc-leptin
  - Pbo: 1 case of cervix carcinoma, 1 case of lung cancer

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/s/  
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11/26/2013

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concur