Risk Evaluation and Mitigation Strategy (REMS)

Prescriber Training Module

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Introduction

Introduction

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

- Prescribers must complete this training module and enroll in the MYALEPT REMS 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.

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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

Serious risks associated with the use of MYALEPT

- Development of anti-metreleptin antibodies that neutralize endogenous leptin and MYALEPT
- Lymphoma

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Antibody Testing in MYALEPT Trials

Data

- As with all therapeutic proteins, there is potential for immunogenicity.
- Anti-metreleptin anti-drug antibodies (ADA) were detected in 84% (36/43) of patients with generalized lipodystrophy studied in the MYALEPT trials.
- Total anti-metreleptin antibody titers ranged between 1:5 and 1:1,953,125.
- Anti-metreleptin antibodies with neutralizing activity (Nabs) were observed in 6% (2/33) of the patients with generalized lipodystrophy tested.

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Antibody Testing in MYALEPT Trials

Data (cont'd)

- Adverse events reported in these two patients included severe infections and worsening of metabolic control (increases in HbA_1c and/or triglycerides) and are consistent with loss of endogenous leptin activity and/or loss of MYALEPT efficacy.
- Physicians are advised to test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of metreleptin efficacy during treatment.

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Boxed Warning

Risk of Anti-metreleptin Antibodies with Neutralizing Activity

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

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Boxed Warning

Risk of Anti-metreleptin Antibodies with Neutralizing Activity (cont'd)

- **In other populations**
  - **3 of 563 patients** who underwent antibody testing
    1. tested positive for anti-metreleptin antibodies with neutralizing activity
    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-metreleptin antibodies with neutralizing activity are not well-characterized at this time due to the small number of reports.

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Testing for 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 Chiesi at 1-866-216-1526 for instructions on how to submit samples for neutralizing antibody testing. The assay is not commercially available.

Chiesi will ask you to:

- Obtain written consent from your patient to release the sample and send a copy of the consent to Chiesi.
- Complete a questionnaire to explain why you are requesting neutralizing activity testing and send it to Chiesi.
- Send the sample to the designated laboratory for testing.
  - The results are generally available within 90 days.
- Chiesi will contact you to provide and discuss the results.

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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.

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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

Appropriate Patient Selection

MYALEPT can only be prescribed in accordance with the FDA-approved indication:

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.

Do not prescribe MYALEPT for any other indications including:

- Treatment of complications associated with partial lipodystrophy
- Treatment of liver disease, including nonalcoholic steatohepatitis (NASH)
- HIV-related lipodystrophy
- Metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of generalized lipodystrophy
- General obesity not associated with congenital leptin deficiency

All healthcare providers intending to prescribe MYALEPT must be enrolled in the MYALEPT REMS and follow the REMS requirements in which physicians attest to the patient having a diagnosis consistent with congenital or acquired generalized lipodystrophy.

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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.

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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

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MYALEPT® (metreleptin) for injection REMS Information

MYALEPT® (metreleptin) for injection REMS

Key Program Elements

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

MYALEPT REMS Goals

The goal of the MYALEPT REMS is to mitigate:

- **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 **the risk of lymphoma**

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MYALEPT REMS Goals

The REMS achieves the goals 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 certification,
- pharmacy certification, and
- *prescriber attestation that each patient has a diagnosis consistent with the approved indication*

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MYALEPT® (metreleptin) for injection REMS Requirements

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 **Prescriber Enrollment Form**.
3. Complete, sign, and submit the MYALEPT REMS **Prescription Authorization Form** for each new prescription.

NOTE: All materials can be downloaded from the MYALEPT REMS website at www.MYALEPTREMS.com or request a copy by calling 1-855-669-2537.

1. Review Prescriber Education Materials

Review the following prescriber education materials:

- MYALEPT® (metreleptin) for injection Prescribing Information
- This Prescriber Training Module

2. Enroll in MYALEPT® (metreleptin) for injection REMS

To enroll in the MYALEPT REMS:

1. Download the MYALEPT REMS **Prescriber Enrollment Form** at www.MYALEPTREMS.com or request a copy by calling 1-855-669-2537
2. Complete the attestations and prescriber information on the enrollment form
3. Sign and submit the enrollment form via FAX to 1-877-328-9682

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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.

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3. Submit Prescription Authorization Form (cont'd)

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

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3. Submit Prescription Authorization Form (cont'd)

- 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.

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3. Submit Prescription Authorization Form (cont'd)

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

1. Download the **Prescription Authorization Form** at www.MYALEPTREMS.com or request a copy by calling 1-855-669-2537
2. Complete the Prescription Authorization Form
3. Sign and submit the Prescription Authorization Form via FAX to 1-877-328-9682

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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 indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.
- ☐ MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with all types of lipodystrophy, including generalized and partial lipodystrophy.

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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 indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.
- ☐ MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with all types of lipodystrophy, including generalized and partial 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)

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Knowledge Assessment

ANSWER

(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.**

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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

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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.

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Knowledge Assessment

3. Developing neutralizing activity to metreleptin could:

- ☐ affect endogenous leptin
- ☐ result in loss of efficacy
- ☐ result in increased susceptibility to severe infection
- ☐ all of the above
- ☐ none of the above

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Knowledge Assessment

3. Developing neutralizing activity to metreleptin could:

- ☐ affect endogenous leptin
- ☐ result in loss of efficacy
- ☐ result in increased susceptibility to severe infection
- ✓ all of the above
- ☐ none of the above

ANSWER

Developing neutralizing activity to metreleptin could affect endogenous leptin and could result in loss of efficacy and could increase susceptibility to severe infection.

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Knowledge Assessment

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

☐ True ☐ False

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Knowledge Assessment

4. If a patient is experiencing severe infections and/or I suspect MYALEPT is no longer working, I will contact Chiesi 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 Chiesi at no cost.

- Call 1-866-216-1526
  - Chiesi will provide you information on the requirements for sample collection and shipment.
- Chiesi will instruct you to:
  - Obtain written consent from your patient to release the sample and send a copy of the consent to Chiesi.
  - Complete a questionnaire to explain why you are requesting neutralizing activity testing.
  - Send the sample and paperwork to the designated laboratory for testing. The results are generally available within 90 days.
- Chiesi will contact you to provide and discuss the results.

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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

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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.

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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 MYALEPT REMS

You have completed training for the MYALEPT REMS.

- To enroll in the MYALEPT REMS, complete the **Prescriber Enrollment Form** and return via FAX to 1-877-328-9682.
- For more information on the MYALEPT REMS, please call 1-855-669-2537 or visit www.MYALEPTREMS.com.